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**WHAT'S NEW IN
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PREVENTION & IMMUNIZATION**

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WHAT'S NEW IN INFECTIOUS DISEASES–PREVENTION AND IMMUNIZATION

FRANCIS J. SWEENEY, JR., M.D., *Guest Editor*

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WHAT'S NEW IN INFECTIOUS DISEASES—PREVENTION AND IMMUNIZATION

Foreword

FRANCIS J. SWEENEY, M.D.

The discovery and the subsequent widespread use of antimicrobial agents during the past 25 years have produced remarkable decreases in the morbidity and mortality of many bacterial, rickettsial and other infectious diseases. Conversely, most viral diseases defy drug therapy and many other types of infectious diseases are poorly controlled by antimicrobial drugs.

During the first four decades of this century great emphasis was placed upon the prevention and control of communicable diseases by isolation and immunization techniques. Events during the antimicrobial era produced a decrease in much of this activity as many individuals erroneously felt that the chemotherapeutic and antibiotic agents would eradicate most, if not all, infectious diseases.

There has been a resurgence of interest in the prevention and immunization of these diseases during the past 15 years. Great advances have been made in control of poliomyelitis and measles. Vaccines have been developed against many of the respiratory viruses and many investigators are attempting to develop effective curative drugs and vaccines for the treatment and prevention of other infectious diseases.

Several years ago, members of the Departments of Medicine, Microbiology and Preventive Medicine at Jefferson Medical College planned a program in which clinically oriented, basic information on the prevention, control, and immunization of infectious diseases would be presented to the practicing physician. Entities were selected which, for the most part, responded poorly or not at all to the available antimicrobial agents.

This symposium represents the fruition of these plans. Written by a distinguished group of investigators, it was presented under the present title in a program held in September 1966 under the auspices of the Jefferson Medical College-Pennsylvania State University Continuing Education Program. It was co-sponsored by the Departments of

Health, the states of Delaware, New Jersey, the Commonwealth of Pennsylvania and the City of Philadelphia. The symposium was made possible by a generous grant from the Foundation for Community Health, Philadelphia, Pennsylvania.

FRANCIS J. SWEENEY, JR., M.D.
Guest Editor

Active Immunization in the Pediatric Age Group

LEWIS L. CORIELL, M.D., Ph.D.*

Infectious diseases killed two out of five children in this country at the turn of the century; the total death rate for children one to four years of age approached 1000 per 100,000 population in 1920,[1] and was higher in New Orleans between 1847 and 1880 (4250 per 100,000).[2] Now, the death rate is less than 100 per 100,000 from all causes, and several causes, including accidents, malignant neoplasms, and congenital malformations, exceed infectious diseases. Control of infectious diseases ranks as one of the greatest achievements of modern medicine. Reduction of deaths from infectious diseases in childhood is certainly the major factor in lengthening life expectancy from 35 to 70 years within the last century.

Immunization is, of course, just one of the many medical advances responsible for this improved life expectancy, but certainly it is one of the major factors. In this report we will review just one preventive measure, active immunization.

This term means stimulation of the body's defensive mechanisms by the introduction of killed or attenuated micro-organisms or their products. The immunity that follows is the result of the active participation of the host tissues and tends to persist for a long time and to rebound quickly upon subsequent challenge by a reinjection of antigen or exposure to the disease organism.

Agents Available

The 18 active immunizing agents now available are shown in Table 1. The first six listed in Table 1 are recommended for all healthy infants and the first nine are frequently administered by pediatricians. The first three are killed vaccines and the next six are living attenuated vaccines. The last group of nine are not recommended routinely but are used in special situations when the risk of infection is apparent.

ROUTINE IMMUNIZATION OF INFANTS

All medical authorities are in agreement that young infants should be inoculated with antigens to increase immunity to diphtheria, tetanus,

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Table 1. *Active Immunizing Antigens Available in 1966*

1. Diphtheria – toxoid	10. Typhoid
2. Tetanus – toxoid	11. Influenza
3. Pertussis antigen	12. Mumps
4. Poliomyelitis	13. Tularemia
5. Measles	14. Typhus
6. Vaccinia	15. Rocky Mountain spotted fever
7. BCG – tuberculosis	16. Cholera
8. Yellow fever	17. Plague
9. Rabies	18. Adenovirus

pertussis, poliomyelitis, rubeola, and smallpox. The composition of the immunizing agents varies somewhat in different countries and by manufacturer but are fairly consistent in the United States because of the Division of Biologic Standards' minimal requirements for licensure. The dosage, route, and spacing of inoculations are varied by individual practitioners and clinics to conform with the disease patterns in their locality and other factors. However, there is remarkable correlation between the recommendations published periodically by the American Academy of Pediatrics, the American Public Health Association, and the Surgeon General's Committee on Immunization Practices. This agreement is not surprising since in each case a committee of specialists constantly reviews the recent advances and issues recommendations based on careful analysis of all aspects of infectious disease control. The recommendations of the Public Health Association and the Surgeon General's Committee cover both children and adults, so, for the purpose of this report on active immunization of the pediatric age group in the United States, we will refer to the recommendations of the Academy of Pediatrics. The Academy issued its first report on routine immunization of children in 1934; its most recent report was issued in July, 1966.[3]

Table 2 shows the Academy of Pediatrics' recommended schedule for active immunization and tuberculin testing of normal infants and children. The dose of immunizing agents for pediatric practice is usually contained in 0.5 ml., but the package circular should always be read and followed if there is a discrepancy with other recommendations. It is recommended that alum-precipitated, aluminum hydroxide- or aluminum phosphate-absorbed diphtheria and tetanus toxoids with pertussis antigen be started at an early age, two months, to stimulate protection against pertussis, which is most severe in the very young. Better antibody response is obtained by delaying inoculations until an older age, but if the initial plus subsequent booster inoculations are given as recommended, a very high degree of protection is afforded, as shown by morbidity and mortality statistics among inoculated children.[4] The first three injections may be given at six to eight week intervals to coincide with a better interval for giving oral polio vaccine at the same office or clinic visit, and many pediatricians and health clinics prefer to start when the baby is six weeks old, at the time of the first postnatal visit. The best schedule for economy of office revisits and rapidity of immunization is to give three doses of DTP and trivalent oral polio vaccine at intervals of six weeks, with a booster dose at 15 to 18 months of age.

Tuberculin tests of the Mantoux type should be used routinely on every child at yearly intervals up to the age of four and thereafter at intervals depending on the risk of exposure to tuberculosis in the area. The purpose of this is to detect infection soon after it occurs so that specific therapy can be instituted early. It is hoped that this will eliminate pediatric deaths from tuberculosis and further reduce the number of open adult type pulmonary infections later on when the child reaches the stresses of adult life.

BCG vaccine is not recommended as a routine for healthy children in the United States because it would convert the tuberculin test and render it useless as a screening test for active infection. BCG vaccine is recommended for children in high-risk groups, such as those unavoidably exposed to infectious tuberculosis in homes, and children living in areas where there is a great deal of tuberculosis among young people.[5]

Live measles vaccine is recommended at 12 months of age as a routine, or as early as nine months of age if there is evidence of a measles epidemic in the area. In the latter case the child may receive another dose later if he does not show evidence of a vaccine take (rash). Either the Edmonston vaccine or Schwarz further attenuated vaccine is acceptable and is followed by immunity to natural challenge for as long as observations have been made, i.e., six and four years, respectively. Booster doses are not recommended because a quick recall of antibody is observed upon reinfection for as long as data have been accumulated. Only time and further study will determine which vaccine gives longer protection and whether booster doses are required. Several alternate

Table 2. *Recommended Schedule for Active Immunization and Tuberculin Testing of Normal Infants and Children**

2– 3 months	DTP, type 1 OPV or trivalent OPV†
3– 4 months	DTP, type 3 OPV or trivalent OPV
4– 5 months	DTP, type 2 OPV or trivalent OPV
9–11 months	tuberculin test
12 months	measles vaccine
15–18 months	DTP, trivalent OPV, smallpox vaccine‡
2 years	tuberculin test
3 years	DTP, tuberculin test
4 years	tuberculin test
6 years	TD, smallpox vaccine, tuberculin test § trivalent OPV
8 years	tuberculin test §
10 years	tuberculin test §
12 years	TD, smallpox vaccine, tuberculin test §¶
14 years	tuberculin test §
16 years	tuberculin test §

Abbreviations: DTP, diphtheria and tetanus toxoids and pertussis vaccine combined; OPV, oral polio vaccine – if trivalent OPV is used, interval should be six weeks or longer; TD, tetanus and diphtheria toxoids, adult type.

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*From Report of Committee on Control of Infectious Diseases, American Academy of Pediatrics, 15th Ed., 1966, p. 5.

†Immunization may be started at any age. The immune response is limited in a proportion of young infants and the recommended booster doses are designed to insure or maintain immunity. Protection of infants against pertussis should start early. The best protection of newborn infants against pertussis is avoidance of household contacts by adequate immunization of older siblings. This schedule is intended as a flexible guide that may be modified within certain limits to fit individual situations.

‡Initial smallpox vaccine may be given at any time between 12 and 24 months of age.

§Frequency of repeated tuberculin tests dependent on risk of exposure of children under care and the prevalence of tuberculosis in the population group.

¶After age 12 follow procedures recommended for adults, i.e., smallpox vaccine every five years and tetanus toxoid booster every ten years as TD.

immunization schedules have been advocated with living attenuated, killed or a mixture of killed followed by living measles vaccine. Killed measles vaccine is not recommended in children except when the live attenuated vaccine is contraindicated, i.e., in leukemia, lymphoma, and other generalized malignancies; in those receiving immunodepressive therapy; and in pregnancy.

A tuberculin test should be done before live measles vaccine is given and those with positive reactions should be placed on antituberculosis therapy before the live measles vaccine is given, or alternately given killed measles vaccine—followed later by living measles vaccine. For infants under nine months of age exposed to measles, prophylaxis with gamma globulin is recommended. The routine use of killed measles vaccine in infants is not recommended for the following reasons: three doses of killed vaccine followed by one dose of living vaccine would be required to insure protection; many clinic patients will not complete such a long series and would therefore not be protected; the expense is increased; more foreign antigen is injected; there are four opportunities for complications, such as accidental introduction of hepatitis virus; and when live measles vaccine is given following killed measles vaccine a local vesicular eruption, rash, and fever have been observed in a small percentage of children. The pathogenesis of this reaction has not been explained. Furthermore, the best way to protect the infant under one year of age from measles is to prevent measles in his older siblings. This can be done by giving one dose of live measles vaccine to all preschool and primary-school-age children who have not had measles. Such a program, if carried out nationwide and followed up each year, would eradicate measles from the country.

Smallpox vaccine is of unquestioned value in protection against virulent smallpox. The protection is relative and gradually declines. Routine revaccination is recommended every five years and more often if smallpox is endemic or if exposure occurs. Medical personnel are at greatest risk of exposure through treating unsuspected cases that arrive in smallpox-free areas by jet plane during the incubation period. The Surgeon General has recommended revaccination every three years for medical personnel.

Complications of smallpox vaccination are quite rare but of sufficient frequency to stimulate continued search for a more attenuated live vaccine or a killed vaccine. So far nothing has been developed that gives adequate protection. The serious complications of vaccination with calf lymph vaccinia virus include encephalitis, vaccinia necrosum, and eczema vaccinatum. The frequency of these serious complications is least if primary vaccination is carried out after one year of age.[6] Therefore, primary smallpox vaccination is recommended at 15 to 18 months of age together with the booster of DTP and trivalent poliovaccine. Complications upon revaccination are very rare.

Vaccines recommended under special situations of exposure in pediatric practice include yellow fever, rabies (duck embryo vaccine), typhoid fever, typhus, cholera, plague, and Rocky Mountain spotted fever. Influenza vaccine is not recommended routinely for normal, healthy children because severe febrile reactions are frequently observed if sufficient vaccine is given to stimulate a good antibody response, and because the disease is usually mild in normal children. Adjuvant influenza vaccines give better response with fever systemic reactions but are not licensed for use in the United States. Children with chronic kidney, cardiac, or lung disease or institutionalized children may be given influenza vaccine preceding seasons of expected high incidence.

Killed mumps vaccine is not very effective and is not indicated in the pediatric age group.

Adenovirus vaccines containing types 3, 4, and 7 have been effective in protecting military recruits but are not recommended for children because these virus strains are not so prevalent in childhood. Types 1, 2, 5, and 6 are more common in infancy but these strains are poorly antigenic when made into vaccines.

The only indication for tularemia vaccine is for laboratory workers or people at occupational risk, e.g., rabbit hunters in endemic areas.

Live attenuated experimental vaccines are under study for rubella, mumps, Mycoplasma pneumoniae, chickenpox-herpes zoster, and selected enteroviruses, and for the many viruses that cause upper respiratory infection, i.e., croup, bronchiolitis, and pneumonia. Pneumonia and influenza grouped together are the greatest cause of child death from infectious diseases today but immunization is still not possible because technical problems remain to be solved and many viruses are responsible for each clinical syndrome.[7, 8]

No vaccines are in prospect for a number of other diseases including viral hepatitis, infectious mononucleosis, cytomegalic inclusion disease, herpes simplex infections, and roseola.

PRECAUTIONS

If properly carried out, prophylactic immunization should be almost completely free from complications. The following points should always be observed.

1. Read the label.
2. Needles and syringes used in immunization should be sterilized before each injection, or, preferably, a disposable syringe and needle should be used, to avoid transmitting viral hepatitis.
3. Clean the skin.
4. Depot antigens should be given intramuscularly.
5. Ask about reactions to previous injections; if there have been reactions, reduce the dose or give small doses of individual antigens.
6. Inject only well infants.
7. Avoid vaccinia in patients with eczema, impetigo, or other open skin lesions.

Immunization of children who are receiving immunodepressive therapy should be delayed if the therapy is short-term. If it is long-term use killed vaccines, followed by a booster of live vaccine later when the child is off immunodepressive therapy.

In summary, I would like to make a plea for immunization of every child in the United States, especially children who do not get regular medical supervision and must be sought out by those who are better informed. This is a concern of practitioners but the primary responsibility falls on public health officials. Maximal protection of all children can be achieved only by combined efforts of all interested groups. The evidence indicates that universal immunization in infancy plus booster doses would eliminate diphtheria, tetanus, pertussis, poliomyelitis, smallpox, and measles. Smallpox has been eradicated from many areas of the world and measles can also be eradicated if the live vaccine is widely used. The only host for the virus is man, and the vaccine confers long-term immunity. Without susceptible hosts the measles virus would not survive. The Committee on Control of Infectious Diseases of the American Academy of Pediatrics has called for elimination of measles by 1970 by use of live measles vaccine.[3] To accomplish this will require vigorous action and cooperative effort of all physicians, health agencies, and the public. An appropriate motto for this campaign has been adopted by the Academy of Pediatrics, "Morbus morbilli periat" (the disease measles, may it perish).

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Rubella and the Rubella Syndrome: Problems and Progress

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The year 1962 was an important one in the history of rubella, for it marked the first isolation of the virus in tissue culture, an achievement reported simultaneously by Parkman, Buescher, and Artenstein,[28] and by Weller and Neva.[44] This discovery opened a whole new era in the investigation of problems relating to the etiology, clinical epidemiology, and immune mechanisms in rubella and the rubella syndrome. The ultimate goal of such investigations is the prevention of maternal infection during pregnancy, for the importance of the disease lies primarily in the teratogenic effects of the virus during the first 12 weeks of intra-uterine life. Although this goal has not yet been reached, a large amount of relevant information has been accumulated,[32] and the first steps toward an effective vaccine have already been taken.[27] This is a remarkable record of achievement for a short four year period.

To go back a bit to the nature and size of the rubella problem, this disease is ordinarily a mild and innocuous infection of childhood, and little attention was paid to it until 1941, when Gregg, an Australian ophthalmologist, recognized the association between maternal rubella and the occurrence of congenital cataracts, heart lesions, and other malformations in newborn infants.[11] The significance of this association in statistical terms was put into perspective by several prospective epidemiologic studies carried out in the 1940's and 1950's in Britain,[23] Sweden,[22] and the United States.[10] The results indicated that when maternal infection occurs in the first 12 weeks of pregnancy there is a 15 to 20 per cent risk of major damage to the fetus.

The long delay in recognition of the teratogenic potential of rubella is related to the epidemiology of the disease. In urban populations it is primarily an infection of school-aged children and significant epidemics occur only every six to eight years. Recent serologic surveys of such populations have shown that by age 15, approximately 80 per cent of persons have been infected, and the percentage of susceptibles falls

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*Professor of Epidemiology and Pediatrics: Attending Pediatrician, Yale-New Haven Hospital off rapidly with each succeeding five year age group.[38] Thus, only when there is a very large epidemic are there enough pregnant women infected to bring the problem of congenital rubella to the surface. This is what happened in Australia in 1940, when a large epidemic occurred following a previous 17 year period of low endemicity. In 1964, in the United States, a similar unusually severe epidemic occurred. As in the Australian one, many pregnant young women were infected, and it is estimated that, as a result, some 10,000 to 20,000 infants born in the United States in 1964 and 1965 suffer today from various defects associated with the rubella syndrome.

CLINICAL EPIDEMIOLOGY

The main clinical features are presented in the upper part of Figure 1. In the typical case, after an average incubation period of 14 to 18 days, there is mild fever, rash, and the familiar lymph node enlargement, characteristically of the postauricular and posterior cervical chain. In children the illness is commonly so mild that the appearance of the rash is the first evidence of infection. In adults, as in many acute viral infections, symptomatology is apt to be more severe: malaise and tender lymph nodes are often noted for several days before the rash develops. The eruption is a maculopapular one that is not highly distinctive and can be simulated by a number of other virus infections associated with rash. In the absence of an epidemic, therefore, it may be difficult to be certain of the diagnosis on clinical grounds alone.

The lower part of Figure 1 shows what has been learned about the pattern of virus excretion and the development of antibodies in relation to the clinical disease. These data have been obtained by examining specimens from naturally occurring cases during epidemics,[16] and by serial tests carried out by Green et al.[9] on specimens from volunteers with experimental infections. A significant feature with respect both to spread of infection to contacts and to infection of the fetus is that viremia and virus shedding from the throat occur as long as a week *before* the appearance of fever and rash. The virus has also been recovered from the stool, and from the urine, around the time of onset. Neutralizing antibody is detectable shortly after the rash appears, and at this time virus disappears from the blood but may persist in the throat for a matter of days, or on rare occasions, for several weeks. Antibodies, detected by the fluorescent technique[4] and by the recently described hemagglutination inhibition (HAI) test developed by Stewart et al.,[39] appear early, at the same time as neutralizing antibody. Complement-fixing antibodies,[36] on the other hand, come up a few days later (Fig. 1).

The pattern of virus excretion indicates a long period of infectiousness. Although the infection is not nearly as contagious as measles, there is good evidence that it spreads readily when there is prolonged exposure, as in a family setting or among recruits living in barracks.[5] Not all infections are clinically apparent, however, and as early as 1953 Krugman et al. demonstrated the occurrence of symptom-free viremia in volunteers experimentally infected.[20] As with other infections, the ratio of apparent to inapparent infection seems to vary with age and other factors. In institutionalized children, a ratio of approximately 1:1 has been observed by Krugman[19] and by our group.[16]

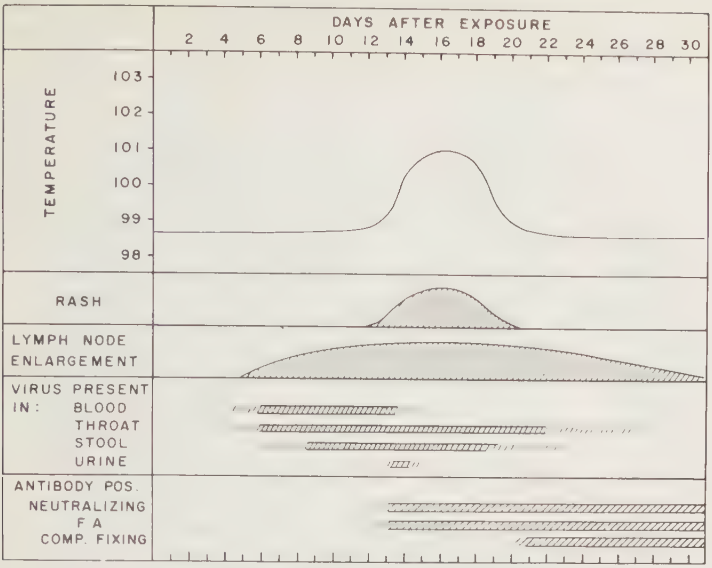

Figure 1. Schematic diagram showing time relationships between clinical signs, virus shedding, and antibody development in typical cases of rubella.

Buescher and Parkman, on the other hand, have demonstrated an incidence of seven inapparent infections for every case among military recruits.[5] A similar ratio in young adults was noted by Brody et al. in an epidemic on St. Paul Island, Alaska.[2]

INTRAUTERINE RUBELLA AND THE RUBELLA SYNDROME

The 1964 epidemic provided an unusual opportunity for examination of fetal and placental tissues obtained at induced abortion at various times after maternal infection with rubella. Virus has been recovered by a number of investigators from amniotic fluid, fetal organs, and the placenta. Alford et al.[1] recovered it from 17 of 27 specimens (63 per cent) obtained up to seven weeks after the appearance of the mother's rash. In some cases, the placenta was positive and the fetal tissue negative, suggesting that infection may be present in the placenta without involving the fetus. Results in our laboratory have been similar: 10 of 18 (56 per cent) specimens of placenta and/or fetal tissue obtained up to eight weeks after maternal infection yielded virus;[15] others have made similar observations.[17, 26, 35] The highest rate of virus isolation is from specimens obtained from women who have experienced rubella in the first eight weeks of pregnancy.

From these and other data it is now clear that maternal rubella early in pregnancy frequently results in chronic infection of the placenta and the fetus. In some cases, possibly when maternal infection occurs later in pregnancy (ninth to sixteenth week) the placenta may be chronically infected without inducing a similar state in the fetus. The relatively high virus isolation rate from fetal tissues during the 1964 outbreak indicated that many intrauterine infections must have occurred, and beginning eight to nine months later, this was confirmed by a

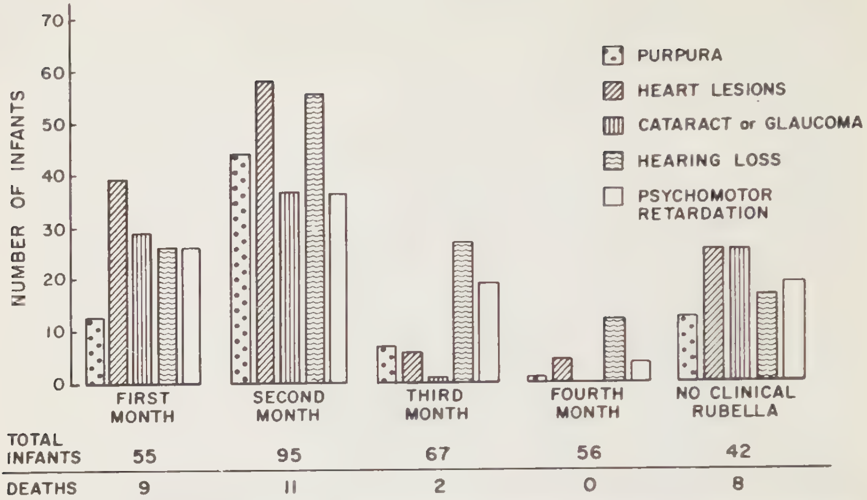

Figure 2. Signs of congenital rubella in 315 infants according to time of maternal infection. (Data from Cooper and Krugman.[6])

virtual epidemic of infants born with stigmata of the rubella syndrome, e.g., congenital cataracts and other eye lesions, heart lesions, and low birth weight. However, one of the most striking features, present in up to 50 per cent, was a petechial-purpuric eruption accompanied by marked thrombocytopenia.[7, 13, 15] This manifestation has been noted only rarely in the past. Another abnormality noted for the first time was radiologic evidence of involvement of the long bones, seen in 20 to 30 per cent of infants.[33] The bone lesions usually disappeared after two to three months. Splenomegaly and hepatomegaly were also observed frequently, and hepatitis with jaundice more rarely.[18, 43] Chronic aseptic meningitis with persistence of the virus in the cerebrospinal fluid was relatively common in some series,[18, 30] but we observed it in only one of 42 infants studied. The list of other anomalies encountered is a long one and involves virtually every organ and system. Impaired hearing (an extremely common problem), defective dentition, and mental retardation cannot be adequately assessed until the children are considerably older, but already 11 of 19 whom we have tested at approximately one year of age have been found to have moderate to severe hearing loss.

Cooper and Krugman have followed more than 300 infants with the rubella syndrome born in the New York City area after the 1964 epidemic.[6] Their data on the association between the time of maternal infection and the type of damage in the newborn infant are summarized in Figure 2. It is apparent that the most serious effects are observed when infection is acquired during the second month of pregnancy. This corresponds well with the time of organogenesis in the human, i.e., between the twentieth and fortieth day of fetal life.[40] As indicated at the bottom of the chart, mortality rates in infants with the rubella syndrome have been high, somewhere between 10 and 25 per cent in the first six months of life. Of 42 followed in our series, eight (19 per cent) have already died as a result of their disease.

In view of the evidence that the fetus suffers a chronic infection,

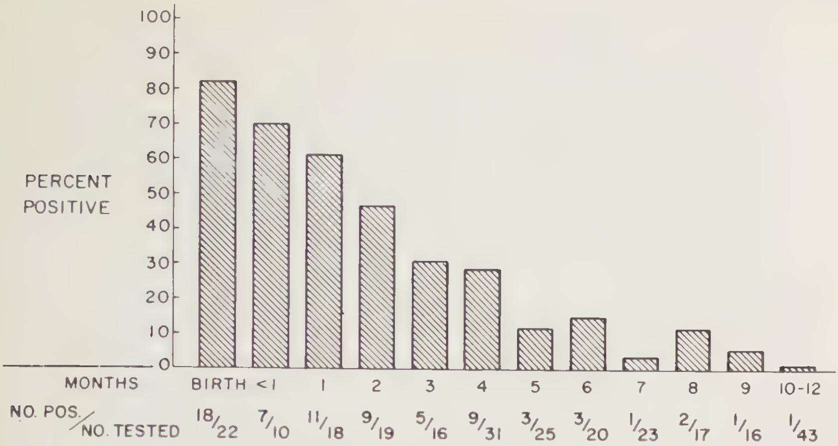

Figure 3. Persistence of virus in the pharynx: results of cultures from 50 infants with the rubella syndrome.

it should not have been surprising that the infant is still infected and shedding virus at birth. Recovery of the agent from the throat, conjunctival swabs, urine, stool, and cerebrospinal fluid have been reported by a number of investigators.[7, 13, 15, 18, 30-33, 43] The throat, however, is the best source of virus. Follow-up studies over a period of months have shown that the percentage of infants with positive throat swabs falls steadily, and by one year of age it is rare to recover virus from them.[8] Figure 3 shows results obtained in our laboratory with specimens collected over a 12 month period from 50 infants. At birth 80 per cent were virus-positive; by six months this had fallen to 15 per cent. By one year, only one infant was still shedding virus, and this child's throat swab was still positive at 16 months of age! Similar results on the gradual disappearance of virus from the throat have been reported by Cooper and Krugman.[8] There is no evidence of long-term (i.e., > 18 months) persistence of virus.[37]

THE PROBLEM OF RUBELLA IN PREGNANCY

Barring the very rare patient who develops one of the severe complications of rubella, the problem presented by the disease relates to the handling of the woman in the first trimester of pregnancy who is exposed to a case or develops a characteristic rash and other signs. If exposure has consisted of contact with a case in the family, usually a child, one can assume that this has been over a period of days and perhaps a week (Fig. 2) before the rash occurred and the diagnosis was made. There is no simple answer as to what should be done in this situation, and the guidelines used to determine whether or not immune globulin (IGG) should be given remain as controversial as before. As to its effectiveness, the work of Green et al.[9] has provided virologic and serologic confirmation of its modifying effect on the clinical *disease*, but demonstrated its failure to prevent *infection*. Antibody-negative, presumably susceptible, volunteers given IGG before inoculation of the virus, or immediately after exposure to an infected person, exhibited viremia, shed virus in the throat, and developed antibodies, even though most of them remained entirely well. There was some suggestion that the duration of viremia was shortened by the use of IGG, but the numbers were small, and firm conclusions on this point are not warranted. The field studies of Brody et al.[3] during an epidemic in Alaska confirm the dampening effect of IGG on clinical manifestations and indicated further that infection could be prevented in a proportion of those exposed. However, in their study unusually large doses of IGG were used (0.25 ml. per lb.) and it is probable that it was given to many children *before* exposure. Taking the available evidence together, it would seem that IGG given after exposure often prevents the disease, and possibly may modify the infection by reducing the degree of viremia, but the result is unpredictable and unreliable, as evidenced by the appearance of frank rubella in women given optimum doses immediately after exposure, as well as by the birth of infants with the rubella syndrome to mothers who have been given IGG at an appropriate time and remained asymptomatic. Therefore, attempted prophylaxis by this method is in general reserved for women in whom, because of religious or other reasons, interruption of the pregnancy would not be considered should rubella occur in the first trimester.

The ways in which laboratory tests can aid the clinician in handling the rubella problem in pregnant women are several. The first is in confirming the diagnosis. Rash and other manifestations of the disease may be extremely mild or atypical, and difficult to distinguish from other exanthems. Isolation of virus from the throat, urine, stool, or blood confirms the diagnosis of rubella. Similarly, if paired blood specimens taken at onset and after seven to ten days or later are tested, the diagnosis may be established by showing a rise in antibody titer. Neutralizing, FA, and HAI antibodies appear early, but the much higher titers of HAI than the others in convalescence make this a more promising test in demonstrating significant rises.[39] Often only a single serum specimen taken during convalescence is available. In this instance the complement fixation (CF) test is the most useful because the CF antibody is a transient one and a high titer suggests recent infection. In contrast, neutralizing, FA, and HAI antibodies persist for many years and their presence may therefore reflect infection in the remote rather than the immediate past.

In the case of the woman merely exposed to rubella, a serologic test can indicate whether she is susceptible or immune. The time required for a conventional neutralization test is two weeks, but with the new HAI test[39] an answer can be obtained within a day. Thus it will be possible to use the results as a guide to whether or not immune globulin is to be given. A positive test, i.e., presence of antibodies in such an early postexposure specimen, provides reassuring evidence of previous infection and immunity. According to data from serologic surveys of urban populations,[38] there is at least an 80 per cent chance of such a happy result in those in the 15 to 19 year age group, and the chance is better with increasing age.

VIROLOGIC ASPECTS AND PROSPECTS FOR A VACCINE

It would seem that the only satisfactory answer to the problem of the prevention of rubella is an effective vaccine that could assure immunity in young women before they reach the child-bearing age. The isolation of the virus in 1962 brought this goal into the realm of possibility, and as a result investigations directed toward developing both killed and attenuated live virus vaccines are being carried out in many laboratories. It was soon found that in addition to culture systems employed in the first recovery of virus, viz., human amnion used by Weller and Neva[44] and primary green monkey kidney (GMK) by Parkman et al.,[28] the virus grows in a variety of other tissue cultures such as continuous line cells of rabbit,[21, 24] baby hamster[11] and monkey tissues,[12, 42] and a variety of primary monkey kidney cultures.[29] In many of these it produces no cytopathic effect (CPE) and in none is the CPE striking and easily recognizable with unadapted virus. In GMK cells no CPE is induced, and the virus is recognized by means of the interference phenomenon; i.e., when GMK cultures are infected with rubella virus they are resistant to challenge with other viruses that normally destroy the cell sheet. The GMK system is widely used for isolation of virus and for demonstration of neutralizing antibodies.

Rubella virus has not proved an easy one to work with, and it has been difficult to attain consistently high titers in the cell systems used. Simple and rapid methods for virus isolation are not readily available; however, the virus has been found to produce plaques in certain cell lines (RK_{13}[24] and BHK[41]) and this provides an important tool for more quantitative assays. Until the recent introduction of the HAI test by Stewart et al.,[39] serologic studies were slow and cumbersome. The neutralization test in GMK or RK_{13} cells requires 12 to 14 days, but a more rapid method employing fluorescent antibody techniques was developed by Brown et al.[4] A satisfactory CF test reported first in 1964 by Sever et al.[36] has been modified to achieve greater sensitivity.[34]

In spite of all the problems, as soon as something was known of the behavior of the virus in various tissue culture systems, efforts were directed toward producing a killed virus vaccine comparable to the inactivated poliovirus vaccine. However, considerable difficulty has been encountered so far in preparing inactivated preparations of high titer that retain significant antigenicity, and to date this problem has not been resolved. Early attempts to produce a live attenuated virus vaccine by serial passage of the agent in green monkey kidney cells were also unsuccessful. Green et al.[9] found that after 25 serial passages, the virus still induced unmodified rubella in vaccinees; furthermore, the infection spread to susceptible contacts. Plotkin et al.[31] have also reported failure to attenuate the virus by several passages in human diploid cells. In the past year, however, substantial progress has been made by two groups of investigators, Parkman and Meyer and their colleagues working at NIH, and Hilleman and his group at the Merck Institute.[14] The only work published in detail is that of Parkman et al., who have reported the successful attenuation of rubella virus by carrying it through 77 serial passages in tissue cultures of green monkey kidney cells.[27] This resulted in modification of the virus as measured by in vivo behavior in experimentally infected monkeys, and by changes in certain characteristics of the virus grown in vitro. Table 1 summarizes some of the results indicating the differences in behavior between low-(4th) and high-(>70th) passage GMK-grown virus inoculated into continuous rabbit kidney (RK_{13}) cultures. The titer and the ability to induce CPE is considerably greater with high-passage material. Low-

Table 1. *Evidence of Modification of Rubella Virus: In Vitro Tests in RK_{13} Cultures**

	LOW GMK PASSAGE (4)	HIGH GMK PASSAGE (77)
Titer by cytopathic effect ($\log_{10}$ TCD_{50}/1.0 ml.)	2.3	4.9
Plaque formation ($\log_{10}$ PFU/0.2 ml.)	<0.0	2.8–3.5
Interferon titer†	<1:4	1:32

*From Parkman, P. D., et al.: Attenuated rubella virus. I. Development and laboratory characterization. New Eng. J. Med. 275:569–574, 1966.

†Determined by vesicular-stomatitis virus plaque-assay method.

Table 2. *Evidence of Modification of Rubella Virus: In Vivo Tests in Rhesus Monkeys**

	LOW GMK PASSAGE (3–5)		HIGH GMK PASSAGE (74)	
	No. Pos./No. Tested	% Pos.	No. Pos./No. Tested	% Pos.
Viremia	12/24	50	0/14	0
Virus in throat	23/24	96	0/14	0
Neutralizing antibody response	24/24	100	13/14	93
Contact infections	2/3	66	0/14	0

*From Parkman, P. D., et al.: Attenuated rubella virus. I. Development and laboratory characterization. New Eng. J. Med. 275:569–574, 1966.

passage virus does not induce plaque formation, but the high-passage virus does; and the amount of interferon produced, as determined in RK_{13} cell cultures with use of the vesicular-stomatitis virus plaque-assay method, is markedly increased at the high-passage level. These characteristics might serve as useful markers in determining the stability of the vaccine strain after human passage.

Table 2 indicates changes that the authors observed in biologic behavior after prolonged passage. Rhesus monkeys inoculated intravenously and intramuscularly with low-passage virus readily became infected: all developed antibody; 96 per cent shed virus in the throat; 50 per cent had viremia; and infection spread to two of three cage mates. In contrast, 13 of 14 animals given high-passage virus developed antibody, but in none could virus be detected in throat or blood, and there was no spread to cage controls.

These encouraging results led Parkman and Meyer to the production of a lot of seventy-seventh-passage virus (HPV-77) which, after appropriate safety testing, was administered to volunteers, who were kept in strict isolation during the observation period. The results reported by Meyer et al.[25] are summarized in Table 3. Two separate trials were carried out, involving a total of 34 susceptible vaccinees and 30 susceptible contacts. Neutralizing antibody developed by the twenty-eighth day in 32 of 34 vaccinees. None exhibited viremia. At least one throat swab from 23 of the 34 (67 per cent) yielded virus, but the number of positive specimens was less than in naturally occurring cases and the titers, in general, were low. None of 30 contacts became infected. An opportunity to document the contrast between the behavior of the HPV-77 strain and wild rubella virus was provided by the appearance of a natural rubella epidemic in the institution in which the studies were carried out. As is usual in "wild" infections, viremia was detected in the pre-eruptive stage, virus was consistently shed from the pharynx, and spread to all 10 susceptible contacts occurred.

These promising results with the HPV-77 virus have set the stage for further investigations of this potential vaccine in larger numbers of people. The prospects for success seem good, yet there are many aspects of the problem that require investigation before a live attenuated virus of this type could be considered safe and desirable. The thought of injecting a live virus vaccine grown in primary monkey kidney cells into hundreds of thousands of children gives one pause. The number of currently known simian agents that must be guarded against in such a product is over 40. Whether there are other, as yet unknown, latent viruses, possibly some with oncogenic potential for man, is an open question that deserves exploration with some of the newer techniques now available.

HPV-77 has been shown to be antigenic, but whether the level of immunity induced will persist and will protect against infection with naturally occurring wild virus strains has not yet been demonstrated, although such tests are undoubtedly currently underway and will continue for some time.

Rubella is peculiar among the infectious diseases in that the ultimate aim of preventive measures is not so much to protect the vaccinee, but to assure a safe environment for the fetus at some future date. Absence of communicability is therefore high on the list of prerequisites for any live virus vaccine. The results with HPV-77 are encouraging on this score, as far as they have gone, but obviously this question will have to be tested in far larger numbers before nontransmissibility can be assured. It is somewhat disturbing that two-thirds of the vaccinees did in fact shed virus from the throat; this raises a note of caution, even though the number of positive specimens from a given person were relatively few and the amounts of virus present were small. It might be argued that even if a pregnant woman exposed to a vaccinee *did* become infected, this would not imply hazard to the fetus, for viremia has not been detected following parenteral injection of HPV-77. Yet

Table 3. *Behavior of Attenuated Rubella Virus (HPV-77) in Vaccinees: Comparison with "Wild" Virus Infections**

	NO. TESTED	ANTIBODY RESPONSE	VIRUS ISOLATIONS		CONTACT INFECTIONS
		Per Cent Positive	Per Cent Positive		
			Blood	Throat	
Vaccinees	34	94	0	67	0/30
Naturally occurring cases	8	100	75†	100	10/10

*From Meyer, H. M., et al.: Attenuated rubella virus. II. Production of an experimental live-virus vaccine and clinical trial. New Eng. J. Med. 275:575–580, 1966.

†Three of four vaccinees tested had viremia.

the virus does appear in the throat, which must mean that there is some degree of viremia below the detectable level with current methods. As mentioned earlier, there is evidence from the data of Alford et al.[1] that the placenta may be a primary site of localization of rubella virus, which then may, or may not, involve the fetus. Töndury,[40] on the basis of detailed microscopic studies of fetal tissues obtained after maternal rubella, has concluded that the endothelial cells of the chorion are the most sensitive to infection, and that infection of the fetus occurs when these cells break off and act as emboli, bearing virus via the blood to the various fetal tissues. Such emboli have been detected in heart, brain, and other organs commonly damaged by rubella virus. If the placenta is such an exquisitely sensitive tissue, the occurrence of any degree of viremia must be considered a hazard until proved otherwise. This is a difficult problem to attack since the only suitable host is the pregnant human. There are circumstances under which, conceivably, such investigations could be carried out, but it will be difficult and time-consuming to arrive at sufficient numbers to assure the safety of a live rubella virus vaccine given to pregnant women. In the meantime, efforts to prepare an antigenic and protective killed virus vaccine are also indicated and will certainly continue.

In spite of the many questions and difficulties that remain, however, the outlook for a solution to the rubella problem in the coming few years is optimistic indeed. Between 1962, when Parkman and Buescher and Weller and Neva first isolated the virus, and the present, 1967, progress has been made at an extraordinary pace. There is reason to suspect that it will continue to do so, and that rubella might soon join the growing list of preventable diseases.

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Measles Vaccines Present Status

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In 1954 measles virus was first isolated in Boston by Dr. John F. Enders and his co-worker Dr. T. C. Peebles,[1] and the way for the development of a measles vaccine was thus paved. In the Boston laboratory, work was soon started to develop such a vaccine, and the outcome was the Edmonston strain of measles virus, a strain that had been attenuated by passages in human kidney cells, human amnion cells, and finally in chick embryo cells.[8] After experiments in monkeys, this strain was studied in susceptible children with excellent results as regards antibody response. About 95 per cent of the children reacted with production of antibodies able to neutralize measles virus.

The side reactions were rather pronounced in these first human studies. The majority (about 80 per cent) of the children reacted with high fever and about half of them with rash. However, there was no doubt that attenuation of the measles strain had taken place, and that the pathogenicity of the virus was low compared to natural measles. Also, the infection was not communicable. But a further decrease in pathogenicity was needed.

Attempts to achieve this have been going on in many laboratories, and several live measles vaccines are now available that have been found to possess a high degree of efficacy and safety.

Inactivated measles vaccines have also been developed, and, as is the case for polio vaccine, both types of vaccines have their ardent advocates. It seems appropriate, therefore, to review the various types of vaccines in an attempt to evaluate their advantages and disadvantages in the light of present knowledge.

REACTIONS AND SERO-CONVERSIONS

Live Measles Vaccines

Attenuated live vaccines were, as mentioned, the first to be tested, and they have been most widely used. The original strain developed by Enders and co-workers[8] has been further attenuated in Great Britain,[6] the United States,[22] and Yugoslavia.[14] Scientists in the Soviet Union and in Japan have developed other attenuated measles vaccines, but it appears that these latter vaccines are not equal to the Edmonston variants in efficacy and safety.

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Table 1. *Natural Measles and Reactions to Live Measles Vaccine*

	MEASLES	VACCINE
Clinical symptoms	85%	4–30%*
Communicability	Marked	None
Morbidity	Major	Minor
Duration	7–11 days	2–5 days
Incubation period	10–12 days	7 days
Complications		
Bacterial	Common	None?
Febrile convulsions	Rare	Very rare
CNS involvement	0.2–2/1000	0.0015/1000?
EEG changes	50–100%	None?

*Up to 90 per cent in virgin populations.

Live measles vaccines are prepared in tissue cultures of chick embryos or canine kidney. The common feature of all these vaccines is that they represent virus strains that have been further attenuated by a variety of laboratory methods, such as tissue culture passages, cultivation in eggs, and variation in incubation temperature. With the present live measles vaccines some children may react with fever, usually of short duration and sometimes with a rash (Table 1). These symptoms are usually transient and mild, with little disability, but on occasion the clinical picture can be more severe.[10]

The great majority of children vaccinated with live vaccines have been found to develop antibodies, which can be measured by a variety of methods, such as neutralization, complement fixation, and hemagglutination-inhibition tests; the latter method is the most sensitive.

COMPARISON OF FOUR LIVE VACCINES IN CONTROLLED TRIALS. The figures obtained with the various live vaccines as regards percentage of those vaccinated who developed antibodies as well as the incidence of undesirable side reactions have varied greatly from one report to another. When a World Health Organization scientific group met in 1963 to consider the problem of measles vaccination,[28] it was decided to set up comparative studies under WHO auspices in five countries, Canada, Czechoslovakia, Nigeria, Switzerland, and Yugoslavia.[3] The following four live vaccines were studied: Enders' Edmonston B vaccine (with or without gamma globulin), and the Schwarz,[22] Beckenham,[6] and Milovanovic[14] strains.

The purpose was to record and compare the incidence and severity of vaccine reactions 5 to 15 days after vaccination and to measure the antibody response in the vaccinated four to six weeks after vaccination. The total number of children in the trials was 1685, and their ages ranged from eight months to three years of age. Two of the vaccines were tested in all five trials, namely, Enders' Edmonston B with gamma globulin and the Schwarz strain. Each trial also included a control group that was given either saline or distilled water instead of vaccine.

The results of the study are interesting in many respects. Considerable variations were recorded and it was found impossible to give exact figures for the side reactions of the various live vaccines.[3] This is perhaps most clearly illustrated by the results from Canada,[16] where the same investigators evaluating the same vaccine recorded rash in 33 per cent of the children in a trial in the spring and in only 3 per cent in a second trial in the autumn.

However, when all data from the five trials were compiled by WHO, the various investigators, on the basis of rash and pyrexia, placed the vaccines in the same order (Table 2). It thus appeared that the fewest high temperatures were caused by the Schwarz vaccine and Enders' Edmonston B vaccine with gamma globulin, but the latter without gamma globulin resulted in the most. The Schwarz vaccine gave a 100 per cent seroconversion rate in all three trials in which it was used, whereas this rate with the other vaccines varied between 85 and 100 per cent.

In addition to these five trials organized by the WHO, one further study may be of interest because it was carried out in a community that has never been exposed to natural measles. In 1965 a total of 422 Eskimos were vaccinated with Edmonston B live measles vaccine* in the Thule district of North Greenland.[15] This area is quite isolated and in 1965 still represented "virgin soil." Exempted from vaccination were all pregnant women and all infants under nine months of age. Clinical data were collected from about 85 per cent of all those vaccinated, and a preliminary evaluation showed that a vast majority of vaccinated persons who did not receive gamma globulin reacted with symptoms of measles, more or less modified. A significant smaller percentage of side reactions occurred in those who received gamma globulin at the time of vaccination (Table 3). It should be stressed that no serious complications were seen. The seroconversion rate was excellent; 99 per cent of those vaccinated developed complement-fixing measles antibodies after vaccination.

Table 2. *Fever 39.4° C. (103° F.) or More in WHO-Supported Studies of Live Measles Vaccines**

	PER CENT
Enders' Edmonston B with gamma globulin	4–38
Schwarz	4–16
Beckenham 20/2	17–20
Milovanović	18–27
Enders' Edmonston B alone	19–58

*From Cockburn, W. C., et al.: WHO-supported comparative studies of attenuated live measles virus vaccines. Bull. WHO 34:223, 1966.

Table 3. *Clinical Reactions to Edmonston B Live Measles Vaccine in a "Virgin Population" of 353 Eskimos in Thule, Greenland, 1965**

	PER CENT REACTIONS	
	> 38.5° C. >101.3° F.	Rash
Children 9 months to 14 years	ca. 75	40–50
Adults, no gamma globulin	ca. 50	40–50
Adults, plus gamma globulin	ca. 25	10

*From Mordhorst.[15]

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*Rubeovax Lyovac, kindly supplied through WHO by Dr. M. Hilleman, Merck, Sharp & Dohme, U.S.A.

Inactivated Vaccines

The inactivated vaccines presently used are prepared from the Edmonston attenuated measles virus propagated either in chick embryo or in monkey kidney tissue cultures.

In comparison with live measles vaccine, there are certain disadvantages and advantages to the use of inactivated vaccine. There are two disadvantages: First, the recommended number of inoculations for the inactivated products is three, plus possibly a booster injection, and the cost of immunization may therefore become considerably higher than for live vaccines. Second, although the seroconversion rate is about the same as for live vaccines, the antibodies may possibly decrease in titer more quickly than those resulting from live vaccines.

The merits of inactivated vaccines are: The inactivated vaccine is easily controlled for safety and potency. It either gives no side reactions or at the worst only very minor local reactions. Inactivated vaccine can be given early in life, for instance at the age of five, six, and seven months (or earlier) during a routine immunization program. Killed measles vaccine can be administered together with other routine inoculations for tetanus, diphtheria, pertussis, and polio, and extra visits to the doctor are thus not needed. Children vaccinated with killed vaccine may on exposure to natural measles or when given live vaccine on rare occasions show a local reaction with swelling on the site of killed vaccine administration. Also, severe atypical measles has been observed in children two to three years after vaccination with killed vaccine.

Inactivated Followed by Live Vaccine

A series of investigators have employed a combination of inactivated and live vaccines in attempts to obtain solid immunity without side reactions caused by the vaccines. As an example, Alexander et al.[1] studied the reactions to live attenuated vaccine in four groups of children: The first group of 58 infants were given three monthly inoculations of inactivated vaccine beginning at one month of age. They were challenged with live vaccine without gamma globulin six months later, when they were nine months old. Another group of 58 infants, six, seven, and eight months old were given a similar course and were also challenged six months later with live vaccine. The clinical reactions to the live vaccine were minimal in both groups.

Two other groups of infants corresponding in age to the first two groups received only live vaccine plus gamma globulin. The side reactions were greater in number and severity and the antibody responses lower (in the youngest antibodies were missing in 25 per cent) than in the two groups of infants given killed vaccine followed by live six months later.

Combined Live Vaccines

Combined live vaccines have not been widely used, but some pilot experiments have been quite promising. For instance, a combination of live measles, smallpox, and yellow fever vaccines was used in 1962 by an American team of investigators in Volta children aged five months to five years.[12] The vaccine was given as jet injection, and there appeared to be no indication that this combination of three live vaccines increased the typical clinical reactions observed with the individual live attenuated vaccines. It was also found that the antibody responses to each of the three components, measles, smallpox, and yellow fever, in the vaccine were satisfactory. A similar study with combined dried live measles-smallpox vaccine has recently been reported.[27]

Combined Inactivated Vaccines

A combination of inactivated measles and polio vaccines has been tested by Warren and Feldman.[26] They gave 133 children three injections of the combined vaccine and found as good seroconversions as when the two components were administered individually. Of the 94 children susceptible to measles, 90 per cent developed neutralizing measles antibodies of good titer. Brown and Kendrick[2] supplemented these studies by giving the combined inactivated measles-polio vaccine to young infants. They were able to show that although the primary antibody responses in some of the children was suppressed by the presence of maternal antibodies, the reaction to booster injections at the age of 18 months was excellent: 95 per cent of the children reacted with formation of both measles and polio antibodies.

The vaccination studies described here are, I hope, representative samples of innumerable studies performed on the problems of measles vaccination. Other investigations describe a great variety of vaccination combinations and contain interesting details, but not all can be covered in this paper.

Longitudinal Studies on Antibodies

Krugman and associates[9] have made a series of interesting studies on the persistence of measles antibodies acquired in different ways, such as maternal antibodies in young infants and antibodies resulting from natural measles. They have also followed antibodies induced by live vaccines, Edmonston B as well as Schwarz' further attenuated strain. In addition, some studies have been performed on antibodies evoked by inactivated vaccine or by a combination of both live and killed vaccine. The antibodies have been measured preferably in hemagglutination-inhibition tests, either the conventional test or by a more sensitive method developed by Norrby.[17]

As for the maternal antibodies, the authors found that of 51 babies only 25 per cent had residual maternal antibodies at six months of age and that all were negative when they were seven months old.

A comparison of measles antibodies following natural infection and those developed after vaccination with live measles vaccines showed that the antibody pattern and the persistence of antibodies were very similar. There was, however, a correlation between the level of antibody and the intensity and frequency of the clinical signs, in that natural measles and live Edmonston B vaccine were found to result in slightly higher antibody titers than live, attenuated Schwarz vaccine or Edmonston B administered together with gamma globulin.

Krugman and co-workers[9] have also studied a combination of killed and live measles vaccines and the influence of the interval between vaccinations. They found that an interval of eight to ten months between the administration of inactivated vaccine and injection of live vaccine is preferable to an interval of one month.

PROTECTIVE EFFECT OF VACCINES

Live Vaccines and Killed Plus Live Vaccines

The protective effect of live vaccines against infection with natural measles has been found to be very high, sometimes 100 per cent in experiments and in smaller trials. It is therefore of considerable interest that a figure of only 85 per cent protection recently was obtained in England in a large field trial comprising approximately 36,000 children between ten months and two years of age.[25] The children were divided in three groups by a random method. One group received one injection of inactivated measles vaccine (Enders' Edmonston B, aluminium hydroxide-adsorbed) followed by live measles vaccine (Schwarz strain) one month later. The second group received live virus vaccine alone, and the third group remained unvaccinated. A representative sample of about 4000 children was selected for study of side reactions during a three week period after vaccination.

Of those receiving only live virus vaccine, 19 per cent were reported to have had a rash in connection with vaccination. The figure was 14 per cent, only slightly lower, for the group having received killed vaccine one month before live vaccine. Rash was recorded in 1 per cent of the children in the control group. The figures for febrile reactions were very low, 6 and 4 per cent for the two vaccinated groups, respectively, but the investigators feel that the incidence of fever is most likely underestimated because temperature was not taken as a daily routine.

Generally it can be said that the vaccine reactions were fewer and milder in the group of children who were given both killed and live vaccine than in those receiving only live vaccine.

As regards the protective effect of the vaccines it was found that during a measles epidemic occurring within six months after the vaccination, the attack rates per 1000 children was 94 in the unvaccinated, 15 in the live vaccine group, and 12 in the children vaccinated with killed and live vaccines. This is a protection rate of 85 per cent, which is certainly lower than usually described. And it may be assumed that this result obtained at an optimal time after vaccination probably represents the maximal protection rates of the vaccines employed. It should be added that these vaccines had been carefully tested for potency before use in the field trial.[25]

The British trial is interesting and important because it confirms that results obtained in small-scale experiments and small trials are not always duplicated when extended to actual field conditions.

Inactivated Vaccines

Results from large field trials elucidating the protective effect of inactivated vaccines are not available, but numerous small-scale experiments have been carried out. The results vary a great deal. Poor protection was found, for instance, in one group of about 300 children aged six months to six years given three injections of killed measles vaccine: 43 per cent of the children developed measles (modified, unmodified, or atypical form) when intimately exposed to measles within about two years after vaccination.[20] However, most investigators have obtained better results with inactivated vaccines.

Among the largest studies is one by Medoff and associates[11] carried out in the Philadelphia area. They gave 964 children aged six months to six years three doses of inactivated vaccine two weeks apart. The children were observed, together with a nonvaccinated control group of the same size, through three successive measles epidemics. The investigators found that whereas 188 of the 965 controls contracted measles, only 11 of the 964 vaccinated children got the disease. This represents a 94 per cent protection rate.

Serologic studies on groups of these children showed that on exposure to natural measles, an anamnestic immune response followed in those vaccinated, with an increase in serum titers indicating a state of immunologic hyperreactivity.

Foege et al.[5] compared 170 children four to five years of age vaccinated three times with inactivated, concentrated measles vaccine with a corresponding group of 158 children given placebo. During a measles outbreak the following season, the vaccine was found to be 93 per cent effective in preventing regular measles and 82 per cent effective in preventing evidence of illness.

DURATION OF IMMUNITY

Natural immunity to measles has been found to last for life, possibly because of reexposure to infection, or even without reexposure. Krugman and others[9] have drawn attention to an observation reported by Panum more than a hundred years ago.[19] During an epidemic in 1846 on the Faroe Islands, where measles had not occurred since 1781, approximately 75 per cent of the 8000 inhabitants got clinical measles, but the incidence and mortality in persons over the age of 65 was found to be lower than in younger age groups, presumably owing to resistance acquired 65 years earlier. Panum's observations were probably correct, but his data are somewhat difficult to evaluate.[19]

Since measles vaccines are able to produce the same level and pattern of antibodies as natural measles, many people seem to expect lifelong immunity after vaccination. This may possibly be true if we can be sure that measles virus will continue to circulate in the child population with subclinical infections bolstering the antibody levels in the vaccinated.

What still seems to be lacking is a direct comparison in a large field trial of the protective effect of live and inactivated measles vaccines, respectively, and of their influence on the circulation of measles virus in the child population. Until such a study has been performed and followed for a number of years, it seems unwise to guess which type of vaccination will turn out to be the most advantageous.

MEASLES IN INFANTS

It is generally known that the most severe complications in measles and the largest number of deaths occur in the age group seven months to one year. It has been shown that although maternal antibodies are not found after six months of age by routine serologic methods, small amounts can be demonstrated by a more sensitive technique.[9] These minute amounts of antibodies may possibly account for the poor effect of live measles vaccine in 7 to 12 month old infants reported by many authors. These antibodies are, on the other hand, insufficient to protect against natural measles, and in Copenhagen the incidence of measles in this age group is as high as in the one to four year old group.[23] In England, in 1961, the fatality rate in children under one year of age without chronic disease was six per 10,000, 20 times the rate in children aged five to nine years.[13]

Inactivated measles vaccine has been found well suited for covering this very vulnerable age between six months and one year, but the schedules recommended for live vaccine administration leaves these infants unprotected.

SPECIAL INDICATIONS AND CONTRAINDICATIONS

Generally it would seem advisable to vaccinate various high-risk groups of people, such as children with chronic diseases of the heart and lungs.

It is considered unadvisable to vaccinate persons with active tuberculosis, unless they are under treatment. Also, one should be aware of possible hypersensitivity to measles vaccine, which is prepared in tissue cultures either from eggs or from dog tissue.

The use of *live* vaccine is contraindicated for persons with leukemia and generalized malignancies, and also during altered resistance from therapy such as steroids, x-ray treatment, antimetabolites and alkylating drugs. Pregnancy is also considered a contraindication, mostly on theoretical grounds. The instructions for use of live measles vaccine are rather elaborate and should be studied carefully before administration of the vaccine.

NEED FOR MEASLES VACCINE

Some developing countries constitute a particular problem because they have a very high measles mortality, especially in children.[7] In Chile, for instance, 42 per cent of deaths in children in their first year of life are reported to be caused by measles, and half of all deaths from acute communicable diseases are due to this illness.[21] Measles vaccines would certainly be of immense value under these circumstances, but the cost involved is likely to be inhibitory, at least for some years.

In more advanced countries, the opinions concerning the advisability of use of measles vaccines vary a great deal. In the United States the Public Health Service Advisory Committee on Immunization Practice has strongly endorsed extensive use of measles vaccine, particularly the live varieties for all susceptible children. By now, more than 10 million American children have been immunized, and the number of reported measles cases has, during the last two years, been lower than in the previous ten years, possibly because of vaccination.

In contrast, the public health authorities in England do not yet seem ready to accept measles vaccination on a *national* scale,[24] although concern about the severity of the disease has been expressed[13] and their large field trial with measles vaccines showed 85 per cent protection.[25]

In other European countries, such as Denmark, the interest is even less pronounced. Usually doctors or parents become excited when they read about new vaccines in journals, newspapers, and magazines, but in spite of the publicity from abroad, we have until now had only three requests for measles vaccine, and two of these came from visiting Americans.

Can this different attitude in the three countries chosen as examples be explained by a difference in measles severity in the three areas? Probably not, but we actually do not know. The death rate from measles seems to be about the same, one to two per 10,000 cases of measles. The figure for encephalitis has been given as ten cases per 10,000 measles cases in the United States and England. In Denmark it is possibly lower, but criteria for a diagnosis of encephalitis may vary.[18] In a large Danish follow-up study, convulsions alone or transitory reflex changes in relation to convulsive fits without paralysis were not regarded as signs of encephalitis.[23] It is of interest that of 59 encephalitis patients, reexamined 3 to 16 years after illness, 40 had recovered completely, physically and mentally. Of the remaining 19, three had grave defects (one cerebral palsy and two mental deficiency), and the rest had medium severe to mild sequelae, two with headache as the only complaint.

Our clinicians and the Danish Public Health Service seem at present to feel that measles is not a disease that would require use of measles vaccines, except perhaps under very special circumstances. Other European countries are apparently interested in the use of measles vaccine for socioeconomic reasons. But the question, "Are harmless childhood diseases really harmless?" does not seem to have been considered very seriously in Europe. It would be interesting to know whether Europeans genetically are more resistant to measles than Americans, or whether Europeans are just more hardy toward the discomforts of their own children.

SUMMARY

Measles vaccines are commercially available in two forms, as live attenuated virus vaccine and as inactivated vaccine. Both kinds have been found to induce seroconversion in a high percentage of susceptible persons, and both have been able to protect up to 85 to 95 per cent of vaccinated persons against clinical measles.

The advocates for *killed vaccines* stress that the antibody levels may often be higher after a series of injections of inactivated vaccine than after the use of live vaccine. Inactivated vaccines do not give adverse reactions, and they can be given simultaneously with other inactivated vaccines and thus be administered with greater ease. They can be employed in infants under one year of age.

For the *live vaccines* it can be said that one dose of vaccine is considered sufficient, less viral material is required, and the live vaccine does possibly induce a broader range of antibodies than the killed vaccines. Also, although live measles vaccines do cause reactions, often considerable, severe complications have rarely been reported.

More than 12 million children have been vaccinated in the United States, mostly with live vaccine, and in the last two years there have been fewer measles cases than in the preceding decade. Outside the United States measles vaccines have so far not been extensively employed.

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Current Problems in the Enteric Infections

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A major source of current problems in the enteric infections is the fact that physicians in the United States no longer consider the acute diarrheal diseases to be a problem. This medical opinion might be warranted if concern were limited by national boundaries or to those diseases seen commonly in teaching hospitals. However, our young physicians are carrying heavy responsibilities in lands far from our own and many of them lack training in dealing with enteric infections. Public health workers are leading major world-wide disease eradication programs, but there are virtually no programs directed specifically toward control of diarrheal diseases, which are the major cause of mortality in most of the developing countries. Investigators are giving scant attention to common enteric disorders, which, in the aggregate, cause a substantial amount of disability.

PROBLEMS RELATED TO MEDICAL TRAINING

In the early fall of 1965, a team of three members of the Commission on Enteric Infections of the Armed Forces Epidemiological Board was requested to visit Vietnam to study diarrheal disease problems among American military personnel. Dr. Horace Gezon, the current Chairman of the Commission, Dr. Franz Ingelfinger, and I were the team members. While my associates visited outlying military installations in Vietnam, I had the responsibility of evaluating the situation in the military hospitals and dispensaries in Saigon.

The chief problem that led to the investigation by the Commission was in Saigon. Although amebic dysentery was being reported with sufficient frequency to indicate that it was a major military medical problem, there was the puzzling fact that virtually all of the hospitalized cases were in one of the two hospitals. Also, it was determined later that one dispensary was finding many cases, and the other three very few. A notable difference in the hospitals was that in one the laboratory was manned by a senior staff of professionals under the direction of an experienced pathologist, whereas in the other the laboratory was run by well trained technicians and a technical supervisor. The dispensary reporting amebic dysentery was the one with a laboratory; it had two technicians, one trained only in an abbreviated course. The medical staffs of these hospitals and dispensaries were preponderantly young physicians having recently completed internships or residencies, and some had excessively heavy clinical loads.

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In the outpatient clinics and dispensaries, the admission clerk gave a container to patients with severe diarrheal disease and directed them to pass a fecal specimen and take it to the laboratory. A technician examined this fresh sample and entered his observations on the laboratory slip, which was taken by the patient to the examining physician. A series of cases had been examined bacteriologically also, but observations were so consistently negative that this procedure had been discontinued.

Records of laboratory findings for preceding months were available. In one hospital, examinations of fecal specimens for Entamoeba histolytica were commonly requested, and over an eight month period, 17.5 per cent were reported as positive. The only technique used was observation of a wet mount, with saline as a diluent if needed. The usual practice was to report simply "E. histolytica found." In only 2 per cent of cases did the report specify trophozoites, though the laboratory chief stated they were observed in many cases. A positive report of "E. histolytica found" was the basis for the diagnosis of amebic dysentery in those with acute enteric symptoms. In the other hospital, less than one-tenth as many fecal specimens had been examined parasitologically and E. histolytica cysts had been found in 2.9 per cent. The examining technique included stained preparations. No patients had been diagnosed as having acute amebic dysentery. In the dispensary with a laboratory, fecal examinations were requested only in the more severe cases and in these, according to the physician in charge, 75 to 80 per cent were reported to be positive for E. histolytica.

In the hospital and dispensary reporting many cases, amebic dysentery was of major interest. The physicians readily commended the laboratory workers and accepted without question the reported findings. On the basis of these observations, patients were put on intensive antiamebic therapy. But when the specimens reported to be positive were reexamined by the author, none were found to be positive. Preserved specimens were returned to this country for competent parasitologic examination and all were negative for E. histolytica. Cellular elements in the feces were being misidentified as E. histolytica; even red blood cells were thought by one technician to be small race cysts.

Before critical thoughts regarding those providing services are expressed, one must consider how this situation could have been modified by more adequate training in enteric infections. There would have been an appreciation at least of the elementary facts regarding acute amebic dysentery. The sudden, often explosive, onsets would have caused this diagnosis to be questioned. Both the clinician and the laboratory workers would have appreciated that in dysenteric stools one would expect to find trophozoites, not cysts, and that typically in acute cases, multiple trophozoites would be found. Furthermore, before diagnosing acute amebic dysentery, the clinicians, both from personal interest and for security in diagnosis, should have taken time to confirm the presence of trophozoites, particularly in a laboratory without senior professional supervision. Even though the clinician might feel hesitant in making microscopic observations, he would recall the distinguishing features of E. histolytica trophozoites, the hyalin pseudopodia, the directional movement, and ingested red cells. But in the situation described, neither the clinicians nor the laboratory workers had clearly in mind such basic information about this acute enteric infection. Their medical training was inadequate for the problem at hand.

Lest it be considered that this was an unusual and atypical situation, let me cite briefly two other experiences. In early 1951, the Commission on Enteric Infections was advised through military channels of the high prevalence of diarrheal diseases among prisoners of war being held by the United Nations forces in Korea. As Chairman of the Commission at that time, I was requested to participate in an exploratory investigation and did so in association with Col. Richard Mason.[3] We were asked to determine whether there was indication for further assistance in control and to assess the possibility of evaluating alternative therapeutic procedures if specific enteric infections were occurring in any substantial number. We anticipated that we would need only to assemble and evaluate the information available. This was at a time when there had been over 20,000 admissions for diarrheal disease to the inadequate hospital facilities that were available. The case fatality rate had been almost 10 per cent. The senior medical personnel were from the United States forces, and before our arrival a special mobile laboratory had been made available to investigate the problem. There was no medical or epidemiologic diagnosis of the situation, nor did we find evidence that would warrant one. The important weakness was the separation of the laboratory in time and distance from the patients. Specific diagnoses were readily available when the microscope and the culture media were taken to the patient, rather than examining specimens supposedly freshly passed but which on later inquiry proved to be hours old. When simple changes in procedure were instituted for those admitted to the hospital for diarrheal disease, 22 per cent were found to have E. histolytica trophozoites, ordinarily present in strikingly large numbers. Of the remainder, 60 per cent were positive for Shigella of 21 types or subtypes and 4.4 per cent for Salmonella, chiefly paratyphi A. The remaining cases were clinically similar to acute bacillary dysentery though bacteriologically negative.

The problems of caring for these prisoners of war were unbelievably difficult. A very large number had been captured over a short period. There had been no prior preparation of facilities or accumulation of supplies because every resource was needed for critical military engagements. The few physicians initially assigned for the care of prisoners of war gave priority to surgical emergencies and had time for little else. But epidemic acute enteric disease was the dominant problem. There was no difficulty in diagnosing cases or identifying epidemics when the facilities available were used in a more effective manner. This had not been done because of deficits in medical training and experience with acute enteric infections.

A further illustration particularly impressed me since it occurred during my introduction to the study of enteric infections. As a young epidemiologist, I was asked to participate in the investigation of the Chicago amebic dysentery epidemic of 1933.[1] As the evidence accumulated, it became apparent that over a period of four months, several hundred persons living in communities scattered throughout the United States had become ill with severe acute amebic dysentery. Seven per cent of the patients died primarily because of misdiagnoses as acute abdominal conditions requiring surgical intervention. Even though those involved were affluent, had patronized a luxury hotel, and were able to seek superior medical care, a very high percentage of the cases remained undiagnosed or inadequately diagnosed until the presumed occurrence of an epidemic of amebic dysentery was made known. The failure of able practitioners to consider the possibility of amebic dysentery in these cases forced one to recognize that there had been virtually no medical education concerning this disease.

My experience impels me to point to gaps in the medical teaching relative to enteric infections; it does not qualify me to suggest remedies. More and more of those trained in the medical schools of the United States are carrying responsibilities for medical care and public health in lands and in environments far different from our own. To an increasing degree, training in global medicine will be required. The lack of effective teaching related to specific enteric infections has had unfortunate consequences. There is no basis for assuming that the need will be less in the future than it has been in the past. Young physicians should be better prepared to be effective in situations such as those cited. For the solution of this current problem in the enteric infections, we must look to modifications of emphasis in general or special medical training.

PROBLEMS RELATED TO COMMUNITY CONTROL

The acute diarrheal diseases either have been or are now a major cause of death in all lands. We may be familiar with the statistics but only rarely do we feel the significance of a persisting excessive mortality from these diseases. One small incident particularly impressed me. In 1964 I spent a few weeks in Libya under the auspices of the USAID public health program. My responsibility was to give advice on the development of public health laboratory facilities. Another consultant was giving attention to hospital administration. With this dual assignment we were visiting all the hospitals. One, more than 100 miles inland from Benghazi, served predominantly the seminomadic Bedouins. The hospital facilities were discouragingly limited and the clinic impossibly overcrowded. There were two well trained physicians. One commented regarding the clinic, "You go till you can go no longer. But you can't see them all." We were having refreshments and a leisurely visit in the home of the senior physician and in this informal setting, I turned the discussion to the diarrheal diseases of the young. There was no need to ask if they were prevalent, so my inquiry was, "What proportion of the infants die in their first year with diarrheal disease?" The younger physician volunteered his opinion, "50 per cent." The more experienced disagreed. "It is higher – 70 to 80 per cent." Speaking with obvious conviction, he cited as an example his experience with infants delivered by cesarean section. It was his expression of deep feeling that impressed me as he said, "Nine of the 12 babies we saved by surgery died of diarrhea before their first birthday."

That diarrheal diseases are preventable is securely established by medical history. Though this cannot be questioned, there is no clear evidence of the relative significance of differing community control measures. Dr. Haven Emerson, commenting on the remarkable decline in deaths from diarrhea and enteritis in New York City during the early twentieth century, suggested that possibly the most significant community measure was the introduction of the automobile. He elaborated to his puzzled listeners, "With this, the stables, the horses, and the flies rapidly disappeared; no longer in the summer and fall was there the ready means of spread of infectious enteric pollutants." There is no evidence to indicate the significance of this or other community changes in reducing the incidence of diarrheal diseases. We know only that with economic development and the building of community facilities and better homes, with social and cultural changes affecting the family, with improved medical and hospital care more readily available, and with the spread of education, these diseases decline. The economic and social evolution that results in prevention comes slowly, even under favorable conditions.

Though knowledge as to the most effective community public health measures for the prevention of the acute diarrheal diseases in areas of high endemic prevalence is inadequate, there is useful guiding information. Epidemiologic evidence has indicated that outbreaks of typhoid fever were often due to pollution of common water supplies, but similar spread of diarrheal disease of known etiology has been demonstrated only rarely. In the control of typhoid fever in the United States, there have been multiple instances of a prompt decline with the provision of safe water supplies to urban communities. But the rapid drop in deaths from typhoid fever was not accompanied by a parallel decline in mortality from diarrheal diseases. The latter receded more gradually. The finding is consistent with the more recent evidence of Watt et al.[6] that the incidence of diarrheal disease is related to availability of water and thus to personal and home cleanliness. There is also the observation in 1948 by Watt and Lindsay[5] that the control of flies by a then effective insecticide reduced the incidence of diarrheal disease by approximately one-half in the test area as compared with the control area. The same communities at different times served both as test and control. There is confirmed medical evidence that the prevention of deaths requires predominantly fluid and electrolyte replacement therapy. Prevention of illness is attained through known practices in infant care and feeding. Progress in control could be attained by community health programs if adequate resources and personnel were directed to this problem.

This nation, having attained leadership in medicine and public health, has accompanying responsibilities. It has contributed to the world-wide control of typhus, malaria, and yellow fever, and the mass prevention of yaws and is ready to aid in the eradication of smallpox. But the public health control of the enteric disorders, which are the major cause of mortality in many lands, has received relatively little direct attention. The application of known control procedures and the search for more specific preventive measures have not been in proportion to the relative magnitude of the need. For the solution of this current problem in enteric infections, we must look to modifications of emphasis in global public health.

PROBLEMS IN RESEARCH

Thus far, comments have been directed to the more severe diarrheal diseases. Turn now to the comparatively mild, the relatively transient and the very prevalent enteric disorders. They have not even attained an accepted name. At one time it was "intestinal flu," but now it is simply "the virus," or "the GI's," or a variety of designations in different localities, such as "gippy tummy" to travelers in Egypt, or "spring diarrhea" at the Clark Air Force Base in the Philippines.

Dr. Charlton Prather sought to obtain a realistic estimate of the cumulative importance of these disorders in Florida. Inquiries in different communities indicated that on an average, each person has such troublesome or disabling symptoms one and one-half days per year. A physician is consulted only rarely. This estimate of incidence conforms closely with the findings of John Dingle and his associates in their exacting studies of illnesses in a group of Cleveland families.[4] They found 1.6 cases of nonbacterial gastrointestinal illness per person year. The symptoms were some combination of vomiting, diarrhea, and abdominal pain. Commonly this was a one day illness; in some it persisted for three or four days. Using Dr. Prather's more conservative rate, six million Floridians have these disturbing and disabling symptoms for nine million days per year, representing about 25,000 person-years. Concerning etiology, there are guesses that these diseases are due to viruses, some of which may be transmitted by the respiratory route. It is general knowledge also that travelers and vacationers are particularly likely to have disturbing bouts of diarrhea which are not due to Shigella, Salmonella, or amebic infections; a sudden and gross change in bacterial enteric flora would be a reasonable hypothesis as to the etiology of these common episodes. One interesting speculation as to the cause of a high prevalence of diarrhea each spring at the Clark Air Force Base was the possible pollution of drinking water with pollens. Clearly, there is no definite knowledge concerning these prevalent though milder illnesses.

The specific enteric infections have commanded the attention of investigators, but currently the total morbidity due to shigellosis, salmonellosis, and amebiasis in the United States is only a small fraction of that due to these ill defined, self-limited, commonly occurring enteric disorders. This is a particularly difficult and unglamorous field of study, but it is a current research problem which is in need of competent and persistent investigation. For the solution of this problem in the enteric infections, we must look to modifications of emphasis in medical research.

SUMMARY

The current problems of enteric infections are not limited by national boundaries; they are global. Physicians and laboratory workers trained in this country are not adequately prepared by either general or special training to handle effectively the clinical and laboratory problems encountered elsewhere. For the highly prevalent diarrheal diseases, public health workers have not evolved specific and rapidly effective community control procedures to be applied under conditions that prevail in developing lands. Known methods of control are not being applied aggressively. At home the important problem is the ill defined milder disorders of short duration and undetermined etiology which in the aggregate cause substantial morbidity. These disorders

need the attention of competent and persistent investigators. For the solution of these multiple current problems in the enteric infections, we must look to modifications of emphasis in medical training, in global public health, and in medical research.

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Typhoid Fever Vaccine—Yes or No?

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Despite numerous evaluations of typhoid vaccine, no other commonly used biologic preventative has raised as much controversy regarding efficacy. Shortly after its introduction by Wright in 1897, it was tested in British troops engaged in the Boer War. This nondefinitive appraisal was the first of many field trials that failed to be conclusive. The incidence of typhoid fever declined steadily owing to clarification of the modes of infection and application of better health practices rather than to the effect of vaccines.

The accumulated evidence of vaccine effectiveness suffered from lack of application of proper controlled techniques. Appropriately, beginning in 1954, the World Health Organization has sponsored well planned field trials in various areas of the world. Field trials are accepted media for vaccine evaluation and are required for typhoid vaccine since the disease is uniquely human. Experimentally produced infections in chimpanzees have clarified some features of the pathogenesis of typhoid fever and of immune relationships. Unfortunately, typhoid bacilli provoke only mild enteric fever in these animals which does not mimic human typhoid fever. Other animals are not susceptible.

WHO-sponsored field trials were initiated in Yugoslavia, Poland, and British Guiana, and induced typhoid studies utilizing healthy inmate volunteers were begun in 1959 at the University of Maryland School of Medicine under the aegis of the Armed Forces Epidemiological Board. Full details of the volunteer studies are presented elsewhere.[5] This presentation summarizes the results of these two differing approaches to the controversial issue of vaccine prophylaxis of typhoid fever.

MICROBIAL AND HOST FACTORS PERTINENT TO PATHOGENESIS

Two factors pertinent to the efficacy of vaccine are the antigenic composition of Salmonella typhosa and those host factors that inhibit or

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Table 1. *Relationship of Number of Typhoid Bacilli (Quailes Strain) to Disease in Healthy Male Volunteers*

NUMBER OF ORGANISMS	NUMBER WITH DISEASE PER NUMBER CHALLENGED
10^9	40/42 (95%)
10^8	8/9 (89%)
10^7	16/32 (50%)
10^5	32/116 (28%)
10^3	0/14 (0%)

enhance spread of the infection. The heat-stable O antigen is in the bacterial cell wall. A rising antibody titer to this antigen is of diagnostic importance in acute infections. Many strains of S. typhosa contain a heat-labile Vi, or virulence, antigen, which presumably envelops the O antigen and may prevent agglutination of the organisms by O antiserum. The Vi antigen is important in pathogenesis of mouse salmonellosis and is regarded as a component necessary for inclusion in an effective vaccine. The flagellar or H antigen has been considered significant for inducing protective antibodies in man.

The volunteer studies showed that typhoid bacilli invade only through the gastrointestinal tract and that organisms survive in the stomach for 30 minutes in spite of low pH. The upper oropharynx and the respiratory tract are unlikely sites of initial invasion; infection does not occur after aerosolization of pathogenic bacilli.

Table 1 shows the number of organisms required to produce attack rates of 25 to 100 per cent in healthy adult males. The ID_{25} and ID_{50} infectious doses of S. typhosa were 10^5 (100,000) and 10^7 (10,000,000), respectively. These rates were determined in those volunteers with disease, which is defined as illness associated with oral temperature of 103° F. or greater for over 36 to 48 hours. Specific treatment was then initiated. Once illness occurred, the clinical courses were identical, regardless of the dose of the infectious inoculum. Only the incubation period varied with size of the infecting dose. There was inverse correlation: longer incubation periods occurred with the smaller doses.

The size of the infectious inoculum was always ascertained in the volunteer trials. In naturally acquired sporadic or epidemic infections, the epidemiologic data must provide this information, which is a conjectural estimation only. In water-borne outbreaks, a pure culture of typhoid bacilli is not ingested. Other bacteria, viruses, or chemicals might be ingested that either enhance or depress the virulence of S. typhosa. Such enhancement has been demonstrated in mice and possibly humans. Bohnhoff and co-workers[2] showed that intestinal flora protect mice from invasion of the intestinal wall by S. typhimurium. Mice pretreated with streptomycin show a rise in pH because of a striking reduction of bacteroides in the colon. Susceptibility is increased 10,000 fold. Volunteers pretreated with oral neomycin or streptomycin were infected with 1000 S. typhosa, whereas no infection occurred without antibiotic administration. Bacterial antagonism in the intestine may be a significant defense mechanism.

Once typhoid bacilli penetrate the intestinal epithelium, they reside intracellularly; this provides protection from effective antibiotic action. Infected mouse fibroblast tissue culture cells withstand the effect of chloramphenicol in the bathing menstruum for as long as 21 days. Following removal of this antibiotic, the organisms again reproduce and are cytotoxic.[4] Pertinent to this point is the observation that human subjects given 3 gm. of chloramphenicol daily for seven days beginning 24 hours after challenge with an ID_{100} dose were not protected from disease; only the incubation period was prolonged. When the antibiotic regimen was extended to 28 days, there was no clinical illness but bacteremia and antibody formation were demonstrated at the same time that they were found in control subjects. Thus, effective chemotherapy for seven days will not prevent typhoid fever if the organism has had 24 hours to localize intracellularly.

ROLE OF HUMORAL ANTIBODIES IN TYPHOID IMMUNITY

There was no correlation in control subjects (nonvaccinated) between the prechallenge titers of O, H, and Vi antibodies and the subsequent clinical course. This was especially true of those volunteers without demonstrable antibodies at the time of challenge with the ID_{25} dose; 36 to 56 men without O antibodies failed to become ill. Nineteen of 38 men with negative H titers failed to manifest disease, whereas only three of 15 with negative Vi antibody titers developed typhoid fever. Obviously humans resist challenge in the absence of conventional humoral antibodies. A search for other circulating immune substances or additional cellular defense mechanisms in noninfected volunteers is warranted.

Immunity following acute typhoid fever is incomplete. Relapses occurred in about 10 per cent of patients before effective chemotherapy was available in spite of high titers of typhoid agglutinins. With antibiotic treatment, this rate has subsequently doubled. This suggests that chloramphenicol inhibits protein synthesis and subsequent production of protective antibody. There is no confirmatory evidence in man for or against this concept. Marmion studied two epidemics of typhoid fever occurring in a British Air Force camp in Egypt.[6] Fifty-four men became reinfected during the second epidemic, which occurred five months after the first. The attack rates were similar regardless of whether chloramphenicol was given in the initial outbreak.

Second episodes of illness in rechallenged volunteers correlated with the dose of typhoid bacilli (Table 1) employed. The role of chloramphenicol in depressing immune responses could not be accurately assessed since all volunteers were treated initially early in their disease. Reinfection did occur, suggesting that the host was unable to establish a high level of immunity consequent to the original infection.

RESULTS OF VACCINE TRIALS

It was anticipated that inactivated vaccines would not produce complete immunity since relapses and reinfections occur in both untreated and antibiotic-treated typhoid patients. Evidence from the World Health Organization trials supported this contention and the volunteer studies provided additional quantitative data.

The test vaccines were produced at WRAIR* from the standard

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*Walter Reed Army Institute of Research, courtesy of Dr. Joseph Lowenthal.

Table 2. *Results of WHO Field Trials with Vaccines K and L—Two Doses**

COUNTRY AND YEARS	AGE AND COMPOSITION	VACCINE GROUPS†			EFFECTIVENESS‡	
		K	L	CONTROL	K	L
Yugoslavia 1960–1963	2–50 years Mainly children	16/5028	37/5068	75/5039	79%	51%
British Guiana 1960–1964	5–15 years School children	6/24046	26/23431	99/24241	94%	73%
Poland 1961–1963	5–14 years School children	4/81534		31/83734	87%	
USSR 1962–1963	School children and young adults		13/36112	50/36999		73%
One Dose of Either Vaccine K or L						
British Guiana 1960–1964	5–15 years School children	0/3319	3/3371	14/3515	100%	78%
Poland	5–14 years	0/9136		3/10067	100%	–

*Modified from data of Cvjetanovic and Uemura.[3]

†Number of cases of typhoid per persons in trial.

‡Effectiveness $\frac{100\,(b-a)}{b}$; a = incidence in vaccinated group, b = incidence rate in controls.

Ty^2 strain. Two types of vaccines, designated K and L, were employed. K vaccine consisted of acetone-inactivated typhoid bacilli which preserved most of the Vi antigen. Vaccine L was produced by conventional heat-phenol inactivation which destroys much Vi antigen. Results of the field trials conducted in Yugoslavia and British Guiana are shown in Table 2.[1, 3] Vaccine K appeared to be more effective than vaccine L in protecting adults. In children, vaccine L was more immunogenic than in adults. Vaccine K again was best in children. These controlled field trials involved large population groups and were subjected to the double-blind technique. The protection reported in these groups did not wane during the three to four year follow-up and one dose of vaccine appeared to give as much protection as two.

In Pristina, Yugoslavia,[9] a high incidence of disease occurred from heavily contaminated water. Those persons *not* volunteering for the typhoid vaccine study had six times the attack rate of the tetanus toxoid vaccine control group (Table 3). These data suggested that those highly motivated persons who volunteered for the study were more concerned with preventive measures and were able to avoid typhoid fever in spite of their failure to receive specific vaccine (placebo group). Despite this artifact, some protection was afforded those persons who received typhoid vaccines.

The volunteer studies have permitted more definitive quantitative estimation of vaccine effectiveness. One strain obtained from a carrier was used, and the exact number of organisms required to infect and the time of challenge were known. Volunteers received the same vaccines employed in the WHO trials. Each received three doses (rather than two), the first two at weekly intervals and the third a month after the second. Oral challenge of viable S. typhosa occurred three months to one year post vaccination. Initially the ID_{100} dose of one billion organisms was employed and no protection was noted, as shown in Table 4. Vaccine-induced resistance to an ID_{50} dose was not demonstrated. By contrast, the infecting ID_{25} dose differentiated the vaccinees from the control group. No difference between vaccine K or L was noted in this study involving adult males. A purified form of Vi antigen was given to a few volunteers who did not show any greater immunity than with the K or L vaccines. Analysis of the base line antibody titers of these vaccinees failed to show any correlation with subsequent immunity. There was no evidence that the course of typhoid fever was mitigated in those vaccinated volunteers who developed disease. The currently available vaccines established protection in volunteers with a vaccine effectiveness of 67 per cent but only against a low dose of typhoid bacilli, 10^5 (based on 27 per cent attack rate in the control group at this challenge level versus 9 per cent in vaccinees).

Table 3. *Typhoid Fever Among the Volunteers and Nonparticipants in a Controlled Field Trial in Pristina, Yugoslavia**

TYPE OF VACCINE	CASES OF TYPHOID NO. OF PERSONS	RATE PER 1000	EFFECTIVENESS
K	13/3346	3.9	70%
L	20/3386	5.9	53%
Control	43/3340	12.9	0
Total volunteers	76/10,072	7.5	
Nonparticipants	777/9500	81.8	

*Modified from data of Yugoslavia Typhoid Commission.[9]

Table 4. *Results of Vaccine K- and L-Induced Immunity in Volunteers Challenged with Varying Doses of S. typhosa*

	CHALLENGE DOSE		
VACCINE	10^9	10^7	10^5
K	2/3*	12/28 (43%)	4/43 (9%)
L	3/4	13/24 (54%)	3/45 (7%)
Vi	6/7	10/14 (71%)	2/13 (15%)
Control	4/4	15/30 (50%)	28/104 (27%)

*Cases of typhoid fever per number of persons challenged

DISCUSSION

Assuming that the results of controlled field trials and volunteer studies are comparable, one can speculate that infecting doses encountered in nature approximate 100,000 organisms, especially in water-borne outbreaks. Since this number of typhoid bacilli causes disease in the minority of exposed persons, perhaps the available vaccines enhance the resistance of this susceptible group so that fewer contract the disease.

Host resistance in infectious processes depends on the interaction of many factors. In typhoid fever the importance of the ecology of the gastrointestinal tract when salmonella are ingested may be of prime importance. The best supporting evidence is derived from the fact that 75 per cent and 50 per cent of unvaccinated control subjects who ingested 100,000 and ten million organisms, respectively, did not become ill. Since little or no evidence of infection occurred in these volunteers, it appeared that the ingested bacteria could not overcome the local defenses of the intestine and subsequently enter the systemic circulation. The mechanisms responsible for this inhibition require clarification. Possible contributory factors operative in the intestine are changes in pH, bacterial antagonism, lysozyme, the effect of colicins or similar substances, tissue and coproantibody, and phagocytosis by epithelial cells.

In some viral infections the presence of circulating antibodies is not necessarily equated with resistance; local antibodies in nasal secretions appear to be most important in protecting the respiratory tract from parainfluenza type I infection.[8] Similar immune substances may be operative in typhoid fever. These and other mechanisms may explain the paradox of the typhoid carrier in whose biliary and intestinal tracts there are large numbers of virulent organisms,[7] yet disease does not occur. Conceivably, children have a less well adapted homeostatic intestinal environment which makes them more susceptible to infection. With increasing age, repetitive nonspecific antigenic and immunochemical experiences may enhance the resistance of the bowel.

SUMMARY

The contribution of vaccines in stimulating host defense against typhoid fever is of minor significance. In certain susceptible populations, it lowers the incidence of disease. There is need for clarification of the mechanisms responsible for defects of acquired resistance in persons who are prone to the disease.

ACKNOWLEDGMENT

We wish to express our warmest appreciation to the volunteers who made these studies possible. Their willingness to participate in these and other similar projects attests to their courage and to the acceptability of the technique. Mr. Vernon Pepersack, Superintendent, and Mr. John Garrity, Warden, are due especial thanks for their continued cooperation.

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Cholera: Whither Prevention?

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During the course of the seventh pandemic of cholera, which has been in progress now for five years, it is important to review the epidemiology of cholera, the measures of control and prevention developed to contain it, and the manner and pattern in which they are being applied. This implies consideration of "what's new" in the field of cholera and how far modern techniques can be effective in the elimination of the infection, first from the areas in which it has been seeded since 1961 and thereafter from the zones of persistent endemicity.

Since cholera broke bounds in the Celebes in 1961 there has not been any significant halt in its progression from country to country, particularly to the west. During this time, despite rigorous quarantine measures, the cholera biotype El Tor has invaded Borneo, mainland China, Macao, Hong Kong, the Philippines, New Guinea, Taiwan, Korea, Singapore, Malaya, Thailand, Vietnam, Laos, Cambodia, Burma, Pakistan, India, Nepal, Afghanistan, Iran, the southern parts of the U.S.S.R. and, most recently, Iraq. There is rightly grave anxiety that this is not the end of the story and that the pattern of past pandemics may be repeated. In these past pandemics cholera has moved insidiously and erratically, keeping no appointments as to time and place until, with the exception of Australia, all continents in the world have been affected to a greater or lesser degree.[20] Further, if past patterns of behavior can be taken as indicative of the future, the present pandemic may be expected to spread still further west and south, continuing over a period of up to 20 years before ecological conditions are such that the infection again dies out in all but the two zones of persistent endemicity, the Indian subcontinent and the Indonesian archipelago. The fact that the biotype El Tor has been predominantly isolated during the current pandemic is of no major epidemiological significance. The disease process to which it gives rise cannot be distinguished from that caused by the classical Vibrio cholerae.[26] In the community the behavior of the El Tor infection is likewise not significantly different.[20] This is cholera. Accordingly, an epidemiological review of the nature of cholera infection and its behavior in the community should not, for the purposes of prevention, differentiate in any practical respect between the two bacteriologically defined biotypes of cholera vibrios.

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Although it is not yet precisely known how cholera is transmitted from person to person, the observed facts substantiate the hypothesis that cholera is a diarrheal disease only of man, that its spread is directly or indirectly by the fecal-oral route, and that if, in this process, a widely used common-source vehicle in the environment inhabited by infected man is heavily contaminated, an explosive common-source epidemic may result. Otherwise, cholera is basically a highly communicable infection of low attack rate that spreads rapidly but unpredictably from person to person throughout a community, with only sporadic cases of recognizable cholera occurring among the cholera prone.[12] Related to these cases are a number of infected persons, some with mild symptoms which are not incapacitating and others without any sign of illness, but all of whom are excreting cholera vibrios apparently as choleragenic as those that can be isolated from overt cases of the disease.[9] These are the carriers who transport the infection from place to place seeding new sources, either human or environmental, as they go. Some of these carriers are intermittent excretors of cholera vibrios over long periods of time and their particular role in the perpetuation of endemicity has not yet been defined.[7] It may be presumed, until proved otherwise, that they are the source of maintenance of endemicity in the region in which they live.

Vibrio cholerae are fragile organisms which will not survive for any epidemiologically significant periods of time under natural conditions outside their normal habitat, the intestinal tract of man. If cholera vibrios are recovered from a water supply or from an environmental source, a meticulous search within the relevant community will uncover an infected human. Similarly, the persistence of V. cholerae in water or other environmental sources is an indication of continuing reinfection by man and does not per se act as a source of the maintenance of cholera infection.[1, 13]

The heaviest contamination of environment arises from seriously ill or fatal cases of cholera. Evidence indicates that the transmission of infection from person to person within this environment is directly related to the degree and duration of physical proximity to the index case. The severity of infection among contacts is unpredictable but appears to be governed by the size of the inoculum received and this is necessarily modified by the social habits of those at risk.[17] For example, last rites practiced without any care for personal hygiene can cause explosive and highly lethal epidemics of cholera among the attendants.[6, 21] Nursing personnel practicing only routine personal or ward hygiene, even in improvised rural treatment centers, can care for very ill or fatal cases excreting large volumes of vibrios without themselves contracting cholera, even though they may acquire an inapparent infection.[2, 3] This leads to the inference that the infection of individuals in a community is governed primarily by the environmental circumstances which determine the size of the inoculum, and not necessarily solely by low socio-economic status. If an unprotected water supply serving an upper class community is heavily contaminated, there is no guarantee that the attack rate and clinical severity of the infection will be otherwise than that expected in a primitive rural township of comparable size with an equally contaminated domestic water supply.

In the same context it is important to recall that laboratory infections do occur – there were two in the United States last year.[43] Further, prior to the general acceptance of the germ theory of disease and of the understanding of the part played by personal hygiene in preventing fecal-oral infections, a number of prominent physicians themselves contracted cholera and some died of it.[illegible] Given a heavy inoculum of cholera vibrios most individuals, even those who are well vaccinated by present-day standards, may be expected to develop signs of the disease.

Under average circumstances of exposure to an index case of cholera, carrier rates in living space contact groups may be expected to range from 7 per cent to over 20 per cent. However, in the total community, overall carrier rates are much lower, being generally 1 per cent or less.[17] Van de Linde and Forbes, following the behavior of sporadic cholera over three years in a densely populated, predominantly urban community of 3½ million in Hong Kong, calculated an overall carrier rate of one in 300 compared to an attack rate of one in 30,000.[11] It is epidemiologically important to note that the majority of carriers are concentrated within the family or living space groups in which the index cases occur.

The duration of the carrier state is generally short, lasting for four to five days on the average. However, Pollitzer has recorded carrier states lasting up to six weeks[illegible] and more recently Dizon has reported a carrier who has excreted cholera vibrios intermittently for over two years.[7]

The problem of the dispersion of cholera vibrios within an infected community thus revolves basically around the movements of symptomless undetected carriers, generally of short duration, who are excreting vibrios which can be as choleragenic in the susceptible host as those emanating from any other sources. Similarly, the problem of dispersion from the infected community across geographic or national boundaries also rests basically with the human carrier, and vehicles of infection other than man have never yet been proved to play a role of any significance in this latter process.[illegible] As Rogers wrote in 1928, "the essential cause of cholera is Koch's comma bacillus and the disease is spread from place to place by human intercourse."[22]

Man is the agent of transmission of infection from country to country and the control of cholera infected man and the management of his immediate contacts and environment are the fundamental measures of prevention.

MEASURES OF CONTROL AND PREVENTION

The Management of the Patient

Modern methods of rehydration and of replacement and maintenance of electrolytes have revolutionized the treatment of cholera.[illegible] Applied within six hours of the onset of severe symptoms, overall case-fatality rates of 2 per cent or less may be expected and even in tented treatment centers in rural areas this has been shown to be possible.[illegible] Accordingly, cholera will not cause the high mortality it did in previous pandemics provided that it is recognized early, is made known as such, and treatment is given promptly. When the treatment by replacement of fluids and electrolytes is reinforced by 4 grams of oral tetracycline, given in divided doses of 500 mg. each for eight doses, the duration and amount of diarrhea will be reduced by 50 per cent and the cholera vibrios will be eradicated from the stool.[27]

Assuming that treatment by rehydration and the replacement of electrolytes can be made generally available as soon as an outbreak of cholera is recognized, the disease itself need not conjure up the dread specter of the past. If, in addition, oral tetracycline can be given in the appropriate doses, the reduction in the duration of inpatient care and the concurrent early abolition of the convalescent carrier state will greatly accelerate the turnover of patients in treatment center beds during the emergency.

The influence of these developments on the control and prevention of cholera merits further emphasis. The priority measure of the health authority faced with a cholera outbreak must be to provide medical teams and facilities for treatment of the sick. These techniques of treatment can be applied effectively in rural areas even under primitive conditions. The early isolation of the index cases in a treatment center and their elimination as a source of infection greatly reduces the quantum of infection in the community or group affected. Equally importantly, the medical teams can be brought at the same time into close relation to the infected family or living space group. Given the necessary additional staff, the medical team is also in a position to undertake responsibility for the two most significant complementary measures of prevention, the management of the contacts of the index cases and of their environment.

In this context of the prompt isolation and treatment of the patient and the management of the contacts, an early presumptive diagnostic technique that can be used at a medical outpost is of first importance. The development of a technique for the rapid dark-field presumptive diagnosis of cholera by Benenson and his colleagues has been a significant advance. Given a dark-field attachment to a microscope, the necessary agglutinating antisera, and a modicum of training and experience of the technique, a presumptive diagnosis of better than 90 per cent of certainty can be made within 10 to 20 minutes of the arrival of a patient at a treatment center.[4] The importance of this technique in investigating not only the index case but an associated contact group needs no emphasis.

The Management of the Environment

This complementary measure to the early recognition, isolation, and treatment of the index case implies concurrent attention to the patient's home environment and his living-space contacts. The living space occupied by the index case becomes heavily contaminated with cholera vibrios, particularly the latrines, drain outlets, cooking premises and utensils.[11] The methods employed for disinfection of the environment remain at the discretion of the health authority concerned and will have to be applied according to the customs and habits of the social groups affected. However, if multiple family infections are to be prevented and common-source sequential episodes avoided, this disinfection must be done comprehensively and as early as possible after the diagnosis of cholera is made. If the living-space contacts are to be quarantined in the dwelling occupied by the index case, as may be necessary under certain circumstances, then the identification and treatment of carriers within that group can also be effected concurrently with the disinfection of the environment. Here reference is again made to the practical importance of the use of the Benenson dark-field diagnostic technique in the management of the contact group.[1]

The Management of the Contacts

This is the crucial area of cholera control and prevention and it presents the greatest challenge to those whose responsibility it is to deal with an outbreak. The majority of symptomless carriers of cholera vibrios are concentrated among the family or living-space contacts of index cases. The longer the duration of that contact the greater the probability of infection.[17] Accordingly, if, during an outbreak, the living-space contacts of index cases are promptly and effectively quarantined and the carriers among them are identified and appropriately treated, that outbreak of cholera will be rapidly contained.

This was first demonstrated by Munson in the Philippines in 1914 and the content of the paper he published subsequently is worthy of close study, setting out as it does much that is pertinent today.[14] Munson recognized the importance of the symptomless carrier state. He realized that the situation is complicated by the presence of carriers of long duration, sometimes excreting vibrios intermittently for many months and most significant of all, and I quote:

> "It is undoubtedly true that the five-day period usually accepted for incubation and quarantine ordinarily will suffice for the control of infection in the majority of cases; but it is equally true that such a period does not hold good in a very considerable number of instances, which sheds much light on cholera situations not otherwise readily explainable."

Nicholls in Ceylon in 1934 also drew attention to the importance of the carrier state, to its duration, and to the incubation period in excess of five days that may take place between exposure to an index case and the recovery of vibrios from the stool of a contact. He documents incubation periods of up to 11 days before stool positivity was established in a group of 13 carriers isolated in a quarantine camp and closely investigated.[15] Kamal in 1950 suggested that the "official" incubation period of cholera should be increased to ten days.[8] More recently, in carriers in Hong Kong, periods of up to seven days, from the initial exposure to stool positivity, have been recorded.[12]

Accordingly, in the management of the contacts of index cases of cholera there are several crucial epidemiological facts to be taken into account. The majority of carriers are among these contacts, they may excrete choleragenic vibrios, perhaps intermittently, for long periods of time, and a quarantine period of five days is not adequate to ascertain whether or not the contacts will become carriers. It is in this area of the management of contacts that the availability of antibiotics, which will effectively and rapidly sterilize the bowel of cholera vibrios, assumes such importance.

During the 1961 outbreak of cholera in Hong Kong, oral streptomycin was given in 1-gm. doses hourly for eight hours on an empty stomach to bacteriologically proved carriers of Vibrio cholerae. This cleared the bowel of cholera vibrios within 24 hours in all but 8.7 per cent of cases. The strains from these latter cases were resistant to streptomycin but all reacted to chloramphenicol given in 250-mg. doses four times daily for five days.[12]

Wallace and his co-workers in Calcutta have given tetracycline to cholera patients in a total dose of 4 gm. given either in two 2-gm. doses on successive days or in 500-mg. doses every six hours for eight doses. This regimen has sterilized the bowel of cholera vibrios within two days without either bacteriological or clinical relapse occurring. Subsequent purging of 29 convalescent patients eight days after the last positive stool culture yielded cholera vibrios in only two of the patients, neither of whom had received antibiotics; the other 27 all had had tetracycline.[27]

However, the administration of antibiotics must be selective and supervised. It is worse than useless to issue vast quantities of untried preparations unselectively to a population group at large. First, there is no guarantee under such circumstances that the preparation will be taken by the individual; next, there is no guarantee that it is effective against the local strain of cholera vibrios or that resistant strains will not appear as a result of inadequate dosage. Accordingly, stress must be on the selective and supervised use of antibiotics for the medication of contact groups either on the basis of treating, preferably, identified carriers or, alternatively, all individuals in the contact group. A scientifically based and comprehensive field trial of the value and role of antibiotics in the management of the family or living space contacts of index cases of cholera in rural areas is not only warranted but is urgent during this period of pandemicity.

Community Measures

Cholera Vaccines. During the past three years scientifically controlled trials of cholera vaccines have been undertaken and assessment of the results has shown that a significant protection against clinically evident illness is conferred on a vaccinated group.[16, 18] The degree of effectiveness varies according to the vaccine preparations used and may range from 50 to 80 per cent of protection. The duration of protection is relatively short and only an oil-adjuvant vaccine used in the Philippines conferred a well maintained protection of long duration. However, the incidence of severe reactions experienced with this oil-adjuvant vaccine makes it unsuitable for general use.[18] For the purposes of this discussion suffice it to say that cholera vaccine prepared to the standards presently advised by WHO and given according to accepted schedules will provide a useful degree of protection to the individual but will not necessarily prevent overt disease in all vaccinated persons.

In considering cholera vaccination as a community measure of control of cholera, however, a realistic view has to be taken. If the vaccine can be given either prior to or very early in an outbreak and given comprehensively to the total group at risk and thereafter repeated at six-month intervals on the same comprehensive scale, then it will be worth while epidemiologically and economically. The number of cases to be treated and isolated will be considerably reduced and the economic benefit of this alone will be considerable. On the other hand, to prosecute a comprehensive vaccination campaign as an emergency measure after an outbreak of cholera has already started must be of limited value in controlling an infection as highly communicable as cholera, particularly if only partial community acceptance is achieved. In either case, as far as is known at present, it is only the incidence of overt disease that is reduced and there is good evidence that the carrier state is not so affected. Night-soil studies in Hong Kong, where there was a comprehensively vaccinated community at the time, indicated that the dispersion of infection was still rapid and widespread.[11] Between 1961 and 1964 studies by the Japanese quarantine authorities revealed 51 bacteriologically confirmed carriers of Vibrio cholerae among individuals coming from a cholera-infected local area but who had satisfactory evidence of vaccination according to international quarantine requirements.[28]

Here is a problem that also warrants intensive investigation if reliance is to be placed on cholera vaccination as other than a supportive measure of control which limits the incidence of overt disease. Until this problem of its influence on the carrier state is resolved, a realistic attitude must be that, while cholera vaccination will undoubtedly continue to be an absolute requirement in any cholera control campaign, its benefit to the community is predominantly related to the fact that it considerably modifies the attack rate of cholera, but only in the vaccinated group. It cannot be expected, in the light of existing knowledge, to have any function in the prevention of dissemination of cholera vibrios either within the infected community or across geographical or national boundaries.

A final point of realism is that the search for other and more effective immunizing agents that will prevent both clinical disease and inapparent infections in the individual is a long-term one. Unless there is an unexpected and major breakthrough in the near future, it will be a number of years yet before immunization against cholera can be established as a fundamental and an epidemiologically adequate community measure of prevention.

Environmental Measures

In all countries and communities, the importance to the public health of protected piped domestic supplies of water and of the control of hygiene in markets and food establishments has been recognized. A great deal has been done in these directions in recent years which is of long-term benefit to the control of diarrheal diseases generally. It is probable that these improvements have, to a material extent, altered the epidemiology of cholera in that the catastrophic explosive common-source epidemics formerly resulting from heavily and continually contaminated water supplies are less frequently seen. As a result, the true sporadic nature of cholera infection has become more apparent.

Nevertheless, no review of cholera prevention is complete without laying full emphasis on the community and individual household measures necessary to ensure uncontaminated water supplies whether piped or from unprotected water channels or wells; this applies equally to the protection of widely used foodstuffs that could become vehicles of infection if heavily contaminated. The measures to be applied are again at the discretion of the responsible health authority, but with good organization and remembering that cholera vibrios are very vulnerable outside their natural habitat, effective disinfection can be achieved under the most primitive of conditions.

Health Education and Public Information

This is a vast subject in its own right and time does not permit of other than brief mention. Always and continuously as a background to any community or international control measures, realistic advice and factual information play a fundamental role in ensuring the success or otherwise of the measures to be applied. The salient points are the reassurance of the public that cholera is not necessarily a fatal disease and that the early reporting and early treatment of suspicious illness can be life-saving. The location of treatment centers, the individual and community measures that are being applied to control the disease, and the necessity for the practice of personal and domestic hygiene are all very pertinent to successful control. One of the new and powerful techniques of public information centers around the use of the transistor radio. From small vessels along the sea coasts, in the backwaters of inland deltas, rivers, and lakes, to nomadic groups in inland deserts, there are nowadays few family groups that do not either have a transistor radio or access to one. Carefully prepared information and advice, which takes into account traditional practices and ways of life, can be beamed to the great majority of groups and communities exposed to the risk of cholera infection today.

International Measures

Chapter II of the International Sanitary Regulations sets out the quarantine and surveillance requirements which have general acceptance by the majority of the countries signatory to the relevant international convention.[29] Briefly, reliance is placed on vaccination against cholera, on the surveillance of travelers coming from cholera-infected areas and on the control of foodstuffs, beverages, and other articles emanating from cholera-infected local areas which are related to suspected or proved cases of cholera.

The emphasis of the Regulations is necessarily on the facilitation of travel, assuming that adequate safeguards exist to prevent the introduction of cholera from infected to noninfected areas. To this end, provided travelers are in possession of valid international certificates of inoculation against cholera, it is only if an individual is both suffering from symptoms indicative of cholera and is within an incubation period of five days since leaving a cholera-infected area that quarantine measures other than surveillance may be applied against him by the health authorities at the point of arrival. Rectal swabbing is prohibited by the Regulations and stool specimens may be required only from a suspected case with indicative symptoms within the incubation period.

Judging by what is known of the duration of the incubation period of cholera infections and by the findings, already referred to, of the Japanese workers who investigated the carrier state in acceptably vaccinated individuals, it is undoubtedly time that these provisions in the International Sanitary Regulations should be critically reviewed. This is particularly so during a pandemic when the total quantum of infection abroad and on the move is so demonstrably uncontained.

No review, however brief, of the international aspects of control is complete without reference to what Shousha called so aptly "cholera hysteria."[24] Action has been taken by health authorities in the past, claimed to be within the provisions of Article 68 of the Regulations, which has resulted in the restriction or banning of commodities coming from cholera-infected areas. These commodities have ranged from postage stamps on first class mail to whole cargoes of mineral ores. As a result, in a number of such instances, grave economic loss has ensued from such actions, taken without due heed to the known facts of the epidemiology of cholera. If, in the future, such problems of restriction or banning arise and rational action is then taken in respect of the humans associated with the articles and cargoes concerned, realistic progress will have been made towards rational prevention. In this respect the use of antibiotics proved effective against cholera vibrios again springs to mind.

Whither Prevention?

To what "point, degree, end, conclusion, or design" is cholera prevention orientated at the present time? The fact that the cholera vibrio biotype El Tor has acted as a marker of pandemic progress is, perhaps, in some ways fortunate. It has shown again that, despite military cordons, sanitary barriers and strict quarantine measures, cholera goes with man, albeit unpredictably and mysteriously. The clandestine traveler, the pilgrim, the traditional boat dweller, and the nomads moving either mounted or on foot are the main agencies which take cholera vibrios through the most rigorously applied defences. Accordingly, the design of prevention must concern itself primarily with man.

The end or conclusion of prevention is clear—first, to control the disease and its transmission within infected communities, then to eliminate it from these communities, and finally to eradicate it from the endemic zones of the world. The point and degree of its application, however, merit a review of existing measures of control of cholera and a coordinated determination, on a global basis, to be done with this disease. The requirements to achieve this coordination are simple, but not easy to achieve.

First, early notification of the presence of cholera is essential. Too often there is doubt, unbelief and perhaps frank panic causing delayed reporting or concealment of its presence. Insufficient bacteriological services is given as a common reason for this lack of early warning and, in many instances, this is true. However, this surely is a difficulty that can be overcome, given the goodwill and determination among the national administrations concerned to make provision of adequate diagnostic services a fully co-ordinated international effort. Awareness of the risk of cholera, early confirmatory diagnosis of its presence, and the immediate and wide dissemination of factual epidemiological information to those at risk are the keystones of success of regional and international action in its prevention.

Next is the degree to which prevention is oriented to the facts of the epidemiology. Regrettably this is the weakest link in the chain. Once the official presence of cholera is announced to the public, vigorous, comprehensive, and costly action immediately ensues. Treatment centers with facilities for effective therapy are marshalled very quickly. Vaccination campaigns are mounted and vast quantities of vaccine are obtained and given. Both are medically sound and are for the good of the individual. Neither, however, go far enough. If the medical teams that are marshalled are given that extra support which will enable them to deal with the family and community aspects of the problem and to work to a prearranged plan of management of the environment of index cases and their living-space contacts, then substantial control will be apparent early and the major quantum of community infection eliminated. The appropriate measures of disinfection and of identification of carriers and their therapy are all known, possible to carry out, and effective. Whatever the cost of these additional measures, it will certainly be less in money, economic dislocation, and human lives than the cost of uncontained cholera.

If cholera is vigorously attacked as a family or living-space group disease of man, then prevention is soundly orientated toward the goal we desire. If it is attacked piecemeal, while uttering shibboleths regarding impossibilities and impracticalities and practicing quarantine measures shown to be ineffective, then we must rely on ecological changes over a period of time to halt the pandemic rather than on the native wit of man.

SUMMARY

The epidemiology of cholera is reviewed in relation to the course of the seventh pandemic of cholera now in progress. Although the cholera vibrio biotype El Tor has been predominant, the clinical and epidemiological pattern of its behavior in the infected community has not been significantly different from that of the biotype causing classical cholera asiatica.

The source of persistence of cholera is the gastrointestinal tract of man and the infection is basically of low attack rate but highly communicable from person to person, with only sporadic cases of recognizable cholera occurring in the cholera-prone. Related to the index cases are numbers of symptomless or unrecognized carriers who are largely concentrated in the family or living-space groups in which the index cases occur. Accordingly, effective control and prevention of cholera rests in the management of these infected groups. Only when common-source vehicles of infection are heavily contaminated, such as water supplies or foodstuffs, do the classic explosive community outbreaks of cholera occur.

Modern treatment by rapid rehydration and replacement of electrolytes, if given early, will reduce the case fatality rate of cholera to 2 per cent or less, even in emergency treatment centers. The addition to the treatment schedule of oral tetracycline in 4-gm. doses given over two days reduces by 50 per cent the duration of therapy and sterilizes the bowel of cholera vibrios. The significance is discussed of the use of tetracycline and possibly other antibiotics in the elimination of the infection from index cases and the carriers in the contact groups.

Cholera vaccines currently in use have been shown to reduce the incidence of overt disease in vaccinated groups by 50 to 80 per cent. Evidence indicates, however, that the vaccine does not reduce the incidence of the carrier state in the community as a whole. As doubt has been cast on the quarantine validity of a five-day incubation period of cholera, international measures of prevention based on vaccination and a five-day incubation period accordingly warrant an early and critical review.

As presently practiced measures of prevention of the dissemination of cholera have not been noticeably successful in halting the progress of the present pandemic, a plea is entered for the management, as a unit, of the infected family group as a fundamental measure of prevention. In this, the use of known effective antibiotics in the elimination of the carrier state has added a new and important weapon of control.

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Viral Agents in Gastrointestinal Disease

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It is well recognized by students of communicable disease that in many cases of infectious gastrointestinal disease (gastroenteritis, enteritis, dysentery, diarrhea) no recognized bacterial, protozoal, or helminthic pathogen can be isolated. Under these circumstances it is tempting for the clinician to ascribe such cases to hypothetical viral agents. This hypothesis seems reasonable when the disease is clearly infectious in nature and a careful search for recognized bacterial, protozoal, and helminthic pathogenic agents has yielded negative results. The studies of Reimann and his associates, of Gordon and Korns, and of Jordan and his associates, among others, lend support to this hypothesis in that these investigators were able to transmit diarrheal disease from patients to volunteers by the ingestion or inhalation of cell-free filtrates of diarrheal stools. The earlier work has been reviewed by Gordon, by Higgins, and more recently, by Reimann and by Cramblett and Siewers. It seems clear, however, that the diagnoses of viral dysentery, viral diarrhea, viral enteritis and viral gastroenteritis are used much too loosely by clinicians, particularly in instances in which no attempt has been made to isolate an etiologic agent. The present situation in gastrointestinal disease parallels that which obtained in the area of upper respiratory diseases a decade ago.

The recent development of tissue culture techniques for the isolation and identification of enteric viruses has placed in the hands of clinicians, epidemiologists, and laboratory workers effective tools for investigating the etiologic role of these agents in the pathogenesis of infectious gastroenteritis and particularly of infectious diarrheal disease. It is the purpose of this paper to review briefly some of the recent studies bearing on this point in order to summarize the present status of viral agents in the pathogenesis of such conditions.

There are three general types of studies which might lend pertinent information on this problem. The first type includes the study of the viral enteric flora of both normal individuals and those ill with manifestations of diarrheal disease. The object of such studies is to show that a viral agent or viral agents may be isolated with some frequency from persons with diarrheal disease while the isolation rate from healthy but otherwise comparable individuals is negligible or at least significantly lower.

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The second type of study includes antibody studies on acute and convalescent phase sera of patients with diarrheal disease. If it can be shown that antibodies against a specific viral agent are formed with some degree of regularity during the course of such an illness, and conversely, that healthy individuals show low or absent titers against it, presumptive evidence of an etiologic relationship between the virus and the clinical manifestations of the disease is at hand. The case is strengthened further if the two types of studies can be combined, viz. the isolation of the agent from cases of diarrheal disease with a fair degree of consistency and the concomitant rise of serum antibodies against the agent, in contrast to a significantly lower isolation rate in normal subjects who show low or absent antibody levels.

The third type of study calls for the isolation of a viral agent from a case of diarrheal disease and the subsequent production of the same clinical syndrome in healthy volunteers by the inoculation (usually by the oral route) of the previously isolated agent. This, when followed by serial passage in volunteers with the consistent production of symptoms of illness, yields the most impressive evidence. As in any experimental procedure using human subjects, the complications and risks are great enough to make this type of approach a difficult one.

It is interesting that nearly all the epidemiologic and etiologic studies (types 1 and 2) have been limited to infants and children and that the viral agents involved have belonged almost exclusively to the enterovirus or adenovirus groups. Of the two groups the enteroviruses (taxonomically representing a subgroup of the picornaviruses of human origin) are more important. Among the family of enteroviruses ECHO viruses appear to play a more significant role in the causation of diarrheal disease than do polioviruses or Coxsackie A or B agents.

A number of studies have concerned the prevalence of enteroviruses in healthy subjects, and in subjects suffering from sporadic or epidemic diarrhea. It has been difficult to compare the results obtained for a variety of reasons. The rapid development of new tissue culture systems during the past three years has meant that the several investigators have used different techniques in many instances. Furthermore, in controlled experiments in which subjects with diarrheal disease have been matched with a comparable group of healthy persons, considerable variation has obtained not only in the selection of the controls but also in the length of time over which the controls were observed in order to rule out the possibility that they had just recovered from the disease or were about to come down with it. A brief summary of some of the more important studies will illustrate these points.

In 1958 Ramos-Alvarez and Sabin compared the prevalence of enteroviruses in a group of 153 children suffering from undifferentiated summer diarrhea with the prevalence of the same agents in 100 "matched" control children who showed no sign of illness. The overall prevalence rate of enteroviruses was considerably higher in those suffering from diarrhea. Although the isolation rates for polioviruses and Coxsackie viruses were the same for both groups, there was a sixfold higher prevalence of ECHO viruses in the group of children presenting signs and symptoms of diarrhea. In the same year Somerville noted a prevalence rate of 21 per cent of enteroviruses among 223 children under five years of age suffering from diarrheal disease, while the comparable rate among 115 "control" children with respiratory disease was 14 per cent. The rates for Coxsackie virus and poliovirus isolations from the two groups were essentially the same; ECHO virus isolations occurred more frequently among the cases of diarrheal disease as compared to those suffering with respiratory disease (5.4 per cent and 2.5 per cent respectively) but the numbers involved were too small to yield a statistically significant difference.

Yow and her associates (1963) compared the isolation rates of enteroviruses from a group of 390 infants with diarrheal disease and a group of 384 matched control infants without manifestations of diarrhea. No significant differences were noted although the isolation rates for recognized bacterial pathogens were quite different for the two groups (22 per cent and 2 per cent respectively). In a continuing investigation involving 180 infants with gastroenteritis and 184 matched control subjects, Yow et al. (1966) obtained similar results. Once more members of the ECHO virus group were isolated more frequently from the sick children but the difference in isolation rates (10 per cent and 4.2 per cent) was not statistically significant. Bacterial pathogens were isolated only from sick children.

Ramos-Alvarez and Olarte in 1964 reported the results of viral and bacteriological studies on 246 children under five years of age suffering from diarrheal disease and on 158 matched control children without diarrhea. Of the children with diarrheal disease 58 per cent yielded viral agents while the corresponding rate among the controls was 21 per cent. The isolation rates for adenoviruses, ECHO viruses, and unclassified viruses were all significantly higher in the group of children with diarrheal disease as compared to the "healthy" controls. Again the isolation rates for bacterial pathogens (Shigella, Salmonella, enteropathogenic Escherichia coli) were significantly higher in the group of children suffering from diarrhea.

These figures for the prevalence of ECHO viruses and adenoviruses in groups of young children, some "healthy" and some suffering from diarrheal disease, are interesting to compare with the results of a survey carried out by Galbraith and his associates in the United Kingdom in 1957–1958. Single stool specimens were obtained from 25,600 presumably healthy children under five years of age. Of these specimens, 25,589 were examined by a variety of tissue culture methods. There were 278 isolations of ECHO viruses, giving a prevalence rate of 1.09 per cent. Adenoviruses were isolated from 128 individuals, giving a prevalence rate of 0.50 per cent. These rates are comparable to those reported by Ramos-Alvarez and Olarte for their "normal" control group of children, but are lower than those noted by other investigators.

The tissue culture methods used in these various studies all differed. Ramos-Alvarez and Sabin (1958) used trypsinized cynomolgus monkey kidney cells as did Somerville (1958). Yow and her associates employed primary monkey kidney cells (species not mentioned) in the first study, and rhesus monkey kidney, human embryonic kidney, and human diploid fibroblast cells in the second study. Ramos-Alvarez and Olarte (1964) used human kidney cells and Galbraith and his group a variety of cells (of which undesignated monkey kidney cells and HeLa cells predominated). Only Ramos-Alvarez and Olarte (1964), and Yow et al.

in their second study (1966) obtained clinical data on the control children sufficient to permit the elimination of those who developed diarrheal disease during the ten days immediately following the time at which the specimen was obtained.

Antibody studies were carried out only by Ramos-Alvarez and Olarte. These investigators tested acute and convalescent phase serum specimens from cases of diarrhea against the viruses isolated from their own rectal swabs. These cases showed a fairly consistent pattern of rise in antibody titer during the period of observation. The "normal" control children rarely showed a rise in titer against the viruses isolated from them.

In several instances of outbreaks of diarrheal disease in young children, etiologic and epidemiologic investigations have incriminated one or more members of the ECHO virus group as the causative agents. The most convincing study is that of Eichenwald and his collaborators who showed that two outbreaks occurring in nurseries for premature infants were due to ECHO virus 18. In both instances the agent was isolated from sick infants but not from well babies. In both instances the infants presenting signs and symptoms of diarrheal disease developed antibodies against ECHO virus 18 during the course of their illness while healthy infants tested during the same time periods failed to do so. Further studies showed that the infection was spread by nursing personnel.

Klein and his associates reported a study of three cases of acute gastroenteritis that occurred in rapid sequence among a group of closely associated laboratory workers. ECHO virus 11 was isolated from rectal swabs taken from two individuals; the third patient was not examined. Acute and convalescent phase serum specimens were obtained from all three patients. In one instance there was no rise in antibody titer, in one, an equivocal rise, and in the third, a definite increase in the level of antibody against ECHO virus 11. Cramblett in 1962 reported a case of laboratory infection with ECHO virus 19 that was accompanied by the development of diarrheal disease in the individual involved. These illustrative studies as well as several similar ones have recently been reviewed by Kibrick (1965).

SUMMARY

1. There is direct evidence that viral agents may cause diarrheal disease in that the ingestion of cell-free filtrates of diarrheal stools by healthy volunteers has been followed by the development of typical disease in them, and in that the agent or agents could be transmitted in series.

2. There is circumstantial evidence (some of it quite strong), implicating members of the enterovirus group as causative agents of diarrheal disease. This evidence has been adduced chiefly from studies carried out in infants and young children. ECHO viruses have been incriminated most frequently, and the evidence is particularly strong in the cases of ECHO 18 and 11.

3. In the vast majority of instances, however, the diagnosis of viral diarrhea, viral enteritis, and viral dysentery is unsupported by scientific evidence. At best it means that no bacterial or protozoal pathogens were detected in the gastrointestinal discharges; at worst, that no laboratory studies were carried out.

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The Influence of Age and Nutrition on the Incidence and Control of Enteric Infections

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In the vast subject which this title comprehends, only general outlines of existing knowledge will be reviewed in order to give some guidelines about control measures. But first we need to define the scope of the subject matter included in the title. Beginning at the end, *enteric infections* includes a wide range of clinical entities ranging from acute diarrheal diseases (infantile gastroenteritis, bacterial food poisonings, cholera, and the dysenteries) to systemic infections like typhoid and paratyphoid fevers, and they also include atypical and inapparent infections by intestinal pathogens; *control* or *prevention* is interpreted as specific and nonspecific measures which contribute through the factors of age and nutrition in reducing both the incidence and severity of enteric infections; *incidence* is concerned with the frequency of occurrence of an enteric infection over a period of time and in relation to the population in which it occurs; it is often expressed as a rate per unit of population per annum; the effect of *nutrition* or *malnutrition* on infection is difficult to disentangle from other personal and environmental factors, e.g., overcrowding, household hygiene, public sanitation, education, and native customs; the effect of *age* will have to be considered in relation to physiologic responses, natural and acquired resistance, exposure to infection, feeding habits, and so forth. It will not be possible to consider all these variables in the whole range of enteric infections, and examples will be chosen from different infections to illustrate specific contributions to knowledge.

WEANLING DIARRHEA

Acute diarrheal disease in the first few years of life is one of the greatest health hazards in the world today. Its ravages are particularly severe in developing countries; e.g., in Central and Latin America in

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1960, over 40 per cent of deaths occurred in children under five years of age and 60 to 80 per cent of these deaths were attributable to the diarrheal diseases. This group of infections may also take a heavy toll in more sophisticated communities; in Portugal, death rates around 2000 per 100,000 infants still occur, compared with rates of 40 to 50 per 100,000 in most other European countries. In many communities there have been dramatic reductions in the past 50 years. In New York death rates from infantile enteritis have fallen from 5600 per 100,000 in 1900 to 45 in 1961.

When intensive microbiologic studies have been made on the acute diarrheas of early life, many different pathogens have been identified—shigella, enteropathogenic Escherichia coli, salmonellae, protozoa, enteroviruses—in 20 to 40 per cent of clinically affected cases and in varying proportions of apparently healthy child contacts. In communities where the disease is endemic or hyperendemic, it is impossible to correlate specific clinical syndromes with particular etiologic agents, so that for epidemiologic and preventive purposes, acute diarrheal disease of early life should be regarded as one entity.

Because this syndrome is most common in the period after breast feeding has ceased to be the only source of nutriment, Gordon and his colleagues[3] have suggested for it the term "weanling diarrhea." The protective effect of breast feeding is probably threefold: it minimizes the risk of ingested infection, it maintains a highly acid reaction in the gut which is presumably protective against ingested pathogens, and it ensures an adequate and well balanced diet for six months or more with normal lactation. This protectiveness is illustrated by data from many different studies, and the peak incidence of weanling diarrhea varies over the age period 3 to 12 months, according to the duration of breast feeding.

Unfortunately, the increasingly prevalent habit in sophisticated communities of artificial or formula feeding of infants from the first few weeks of life is too frequently adopted in the developing countries for a variety of reasons. As a result the infant is exposed to extraneous infection, the protein-caloric intake is reduced, and diarrhea occurs at an early age when the child is ill adapted to cope with it.

In the absence of early and effective rehydration, the case mortality from acute gastroenteritis has a direct relationship to the age of onset, as the data in Figure 1, representing the findings in London hospitals in the five-year period 1933 to 1937, illustrate. The sharp decline in both the incidence and severity of infection from the second year of life onward (Table 1 and 2) raises the question as to whether this is due to an increase in natural resistance or to the development of a more specific immunity. Clinical infection with the enteropathogenic E. coli types is rare after the second year of life but may manifest itself in older debilitated persons. This age limitation suggests that there may develop local protective mechanism in the gut. There is some analogy in the high susceptibility of suckling rabbits to experimental cholera, which rapidly declines 12 to 15 days after birth. Dutta and Oza[2] found that the cholera "enterotoxin" was detoxicated by treatment with acid-buffered extracts of adult rabbit bowel mucosa but not by the corresponding extract from baby rabbits; and also that the toxin was inactivated by the enzymes lipase and phosphorylase but not by pepsin or trypsin. We have had somewhat similar findings with a partially

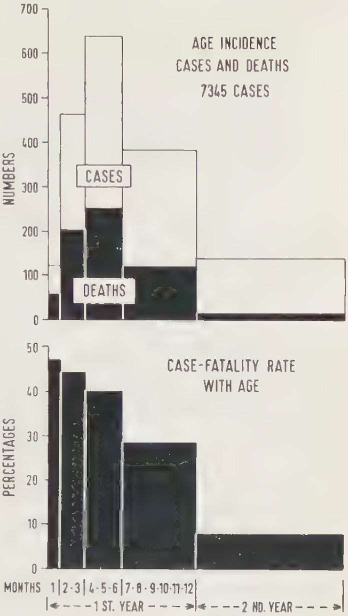

Figure 1. Showing above the number of cases and deaths at different age periods; below, the decline in case-fatality with age. (London C.C. Hospitals, 1933–1937.)

Table 1. *Attack Rates: Cases of Acute Diarrheal Disease per 100 Persons per Year by Age, Four Guatemalan Villages, 1956–1959**

AGE GROUP	NUMBER OF PERSONS	CASES OF DIARRHEA	ATTACK RATE CASES/YEAR/100
0– 5 months	92	43	46.7
6–11 months	79	87	110.7
1 year	135	162	120.0
2 years	122	129	105.7
3 years	119	66	55.4
4– 6 years	406	86	21.2

*From Gordon, J. E., and Scrimshaw, N. S. (1965).

Table 2. *Deaths from Diarrhea, under Five Years of Age, Colombia, 1960**

AGE	NUMBER	PER CENT IN AGE GROUP		AVERAGE PER CENT PER MONTH IN AGE GROUP
Under 28 days	1,187	6.0	57.5	6.0
1– 5 months	4,932	24.8		5.0
6–11 months	5,303	26.7		4.4
12–23 months	4,840	24.3	42.5	2.0
24–59 months	3,634	18.2		0.5
TOTAL	19,896	100		(3.32)

*From Gordon, J. E., and Scrimshaw, N. S. (1965).

Table 3. *Cases of Diarrhea Among Children from Birth to Four Years and Attack Rate per 100 Persons per Year by Nutritional State, Guatemala**

NUTRITIONAL STATE	NUMBER OF CHILDREN	NUMBER OF CASES	CASES PER 100 CHILDREN PER YEAR
Normal	25	35	98.8
1st degree malnutrition	74	172	164.1
2nd degree malnutrition	71	254	252.5
3rd degree malnutrition	9	35	274.5

*From Gordon, Guzmán, Ascoli, and Scrimshaw (1964).

Table 4. *Cases of Severe Diarrheal Disease Among Children from Birth to Four Years, by Nutritional State, Guatemala**

NUTRITIONAL STATE	CASES OF ACUTE DIARRHEAL DISEASE	SEVERE CASES	PERCENT SEVERE CASES
Normal	35	8	22.9
1st degree malnutrition	172	65	37.8
2nd degree malnutrition	254	74	29.1
3rd degree malnutrition	32	14	40.0
Malnutrition, all degrees	461	153	33.2

*From Gordon, Guzmán, Ascoli, and Scrimshaw (1964).

purified cholera "exotoxin." Since the pathogenesis and pathology of weanling diarrhea have resemblances to cholera, a similar protective mechanism may develop with age against the "toxins" of infantile enteritis.

Because of the multiplicity of etiologic agents, it is difficult to believe that the acquisition of a more specific immunity plays a significant role in the restricted age incidence of weanling diarrhea, although the steady increase with age of the carrier:case ratio in bacillary dysentery suggests that in this specific infection, acquired immunity plays its part. We shall return to this problem in the discussion on cholera.

A relationship between infection and nutrition has long been suspected in weanling diarrhea but specific proof has been lacking. The recent studies by Gordon and Scrimshaw,[4] working in Guatemalan villages under INCAP, have furnished useful positive evidence. By classifying young children into three categories of malnutrition according to the percentage below expected weight, these authors found that both the incidence and severity of acute diarrheal disease showed a close correlation with the degree of malnutrition (see Tables 3 and 4).

It is evident from studies in many lands that the nutritional status of the young child begins to deteriorate from the time of weaning and the substitution of other foods. Besides the new exposure to extraneous infection, the resultant malnutrition lowers the child's resistance and a vicious cycle sets in. The diarrheal episode leads to further malnutrition because of lessened appetite, the use of diluted and less nourishing food, and the increased metabolic loss, so that further attacks of diarrhea are frequent. In the baby this often leads on to marasmus and in the toddler to kwashiorkor.

Lest we become too complacent I would point out that sophisticated countries like the United States and the United Kingdom still face the problem of weanling diarrhea, with the same epidemiologic features, despite the remarkable decline in magnitude in these countries over the past 50 years. For example, the incidence of infantile diarrhea associated with specific E. coli types is much higher in the industrial conurbations of England and Wales than in the less densely populated areas.

SALMONELLA INFECTIONS

Infections with salmonellae fall into two broad categories – acute gastroenteritis of the food-poisoning type and systemic infections like typhoid and paratyphoid fevers. But, as Newell[5] points out, there is a gradient from symptomless excretor to systemic fever: the latter syndrome (enteric fever) is associated particularly with salmonella types whose natural host is man, whereas the food-poisoning types have their reservoir in various animal species.

The incidence of infection with the food-poisoning salmonellae is highest in infancy and declines steadily with age. The fatality rate is also highest in infants. It is not likely that this age distribution is related to the acquisition of specific immunity, nor does it have a close relationship to the degree of exposure to infection. Rather it suggests that the infant has a naturally high susceptibility to salmonella infection. This viewpoint is supported by the occurrence of salmonella diarrhea as a hospital cross infection in pediatric units. Here the infecting dose must be very small since the vehicle is not usually food, whereas in typical outbreaks of salmonella food poisoning the infecting dose is very large. Paratyphoid fever has a somewhat similar epidemiology. It may be noted that the period of convalescent carriage of the infecting salmonella is much longer in young children than in older age groups.

In communities where typhoid fever is endemic, the attack rate is highest in the age range 2 to 15 years, and this infection seems to be rare in infancy. The lower incidence in older age groups may be related to the development of immunity in endemic areas. In contrast to salmonella food poisoning, the case mortality from untreated typhoid fever increases steadily with age. This is, of course, a phenomenon seen in other specific infections like lobar pneumonia and typhus; but it is surprising that this rise in fatality rates may begin as early as the second or third decade of life. Malnutrition is probably not an important factor in the incidence of salmonella infections although it almost certainly affects the severity of infection.

CHOLERA

The recent spread of cholera to many countries which have been

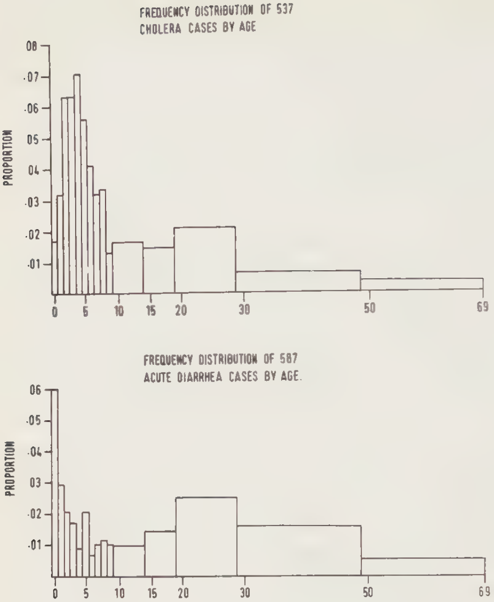

Figure 2. Charts illustrating the differences in age frequency distribution of cholera and acute diarrhea. (Cholera Research Laboratory, Dacca, East Pakistan, Capt. R. M. Phillips, Director.)

free of this infection for the past half century is associated with the El Tor variant and naturally raises fresh interest in the epidemiology of the disease. For various reasons, patients with cholera admitted to hospitals have included more adults than children, so that inaccurate records about age distribution of cholera have been reported. From the recent studies into the epidemiology of cholera organized by the staff of the Cholera Research Laboratory at Dacca, East Pakistan, it is apparent that about two-thirds of the clinical cases in an endemic area occur in children under 15 years of age, with a peak at ages two to six years (Fig. 2). The close bunching of cases when multiple infections occur in a family (Fig. 3) indicates a common source vehicle such as food, and as the staple communal diet in these families is rice, the high incidence in children suggests a greater susceptibility of the younger age groups. Fortunately, there are now records of antibody levels to the cholera vibrio in a cross section of the community around Dacca and these indicate that the incidence and titer of specific antibody increase quite remarkably with age (Fig. 4). In contrast to the age distribution of other diarrheal diseases in the same area (Fig. 2), cholera seems not to affect the infant to any extent and the rapid decline in incidence from six years of age onward is probably most closely related to the development of specific immunity from latent infections.

What, if any, is the relationship of malnutrition to cholera? The infection undoubtedly has its highest incidence in poor-class crowded communities and seems often to have a selective affinity for individual members in a family. The similarity in its pathology to nonspecific weanling diarrhea has been pointed out by Dammin et al.,[1] and since malnutrition is probably a contributory factor in the pathogenesis of the latter syndrome, it may be that it plays a part in the etiology of cholera. Biopsies of bowel mucosa from affected patients have shown very little

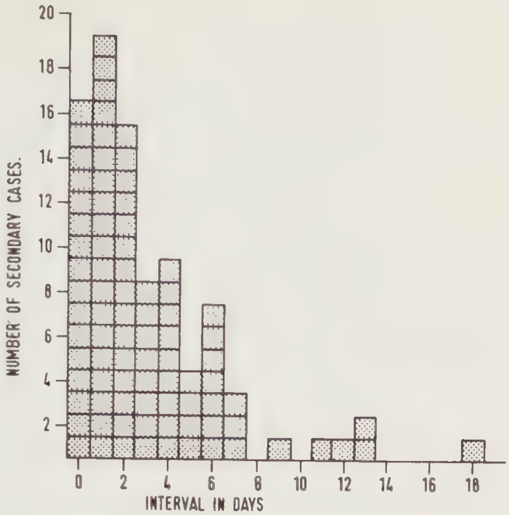

Figure 3. Interval between onsets of index and secondary cases in 58 families with multiple cholera cases. (Cholera Research Laboratory, Dacca, East Pakistan, Capt. R. M. Phillips, Director.)

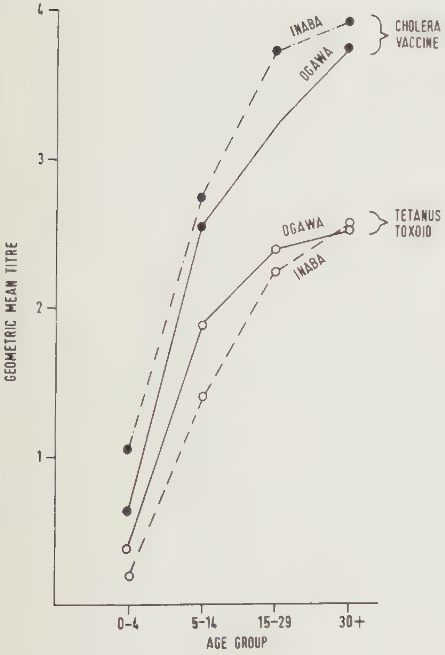

Figure 4. Geometric mean vibriocidal titers by age group in the populations that received cholera vaccine and tetanus toxoid, 1964. (Cholera Research Laboratory, Dacca, East Pakistan, Capt. R. M. Phillips, Director.)

abnormality apart from some "flattening" of the mucosal cells, which may be an expression of malnutrition. The evidence is inconclusive.

SHIGELLOSIS

Although I prefer the term bacillary dysentery to shigellosis, I must admit that much of the present-day infection by the shigella family has little resemblance to the "bloody flux" of biblical times. Although dysentery seems to flourish where hygienic standards are low, we in Britain are concerned at the apparently anomalous phenomenon of increasing waves of Sonne dysentery affecting the whole country over the past 30 to 40 years (Fig. 5).

The epidemiology of this infection has many fascinating facets that cannot be discussed here (but see Taylor[6]). I shall refer only to the age distribution. As has been aptly said, "The scourge of armies has become the bane of nurseries." During and after the Second World War, when day and residential nurseries became greatly extended in the United Kingdom, dysentery had its peak incidence in those two to four years of age; later, with a sharp fall in the number of day nurseries, the peak changed to age five to seven years. This changing age distribution was undoubtedly related to the risks of exposure to infection and the standards of personal hygiene and environmental sanitation among children attending primary schools. Interestingly, as in cholera, babies up to 12 months of age seem to be less affected than toddlers, despite close family exposure. Thus, age per se does not seem to be a dominant factor in the incidence of bacillary dysentery, although in hyperendemic areas, the higher ratio of clinical to carrier infection in the younger age groups is probably related to the gradual development of acquired immunity.

The difficulty of disentangling malnutrition from other concomitants of poverty again confuses the picture about its relationship to the incidence and severity of shigellosis. The epidemics of bacillary dysentery in mental hospitals during periods of war when food supplies, including fresh vegetables, are restricted, suggests a relationship to malnutrition, but other etiologic factors may be involved. On the whole,

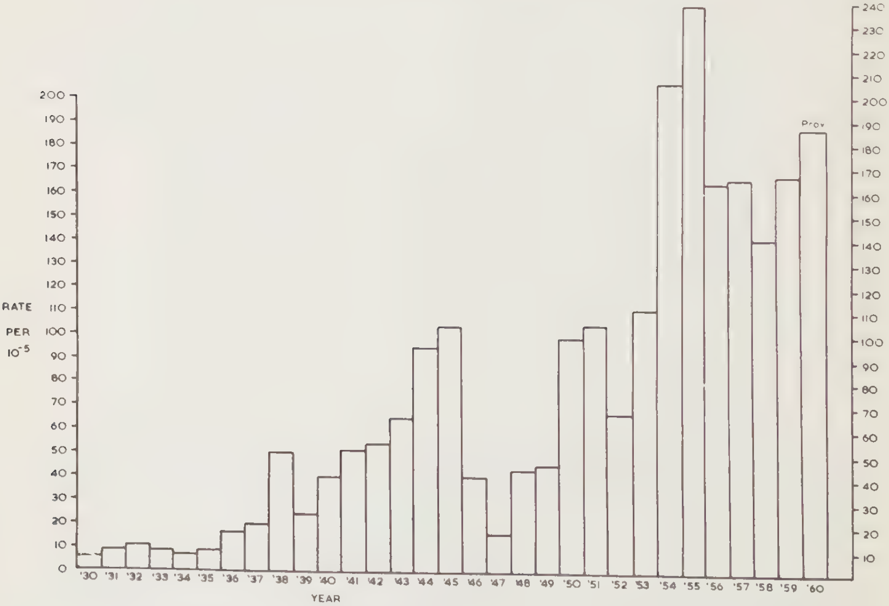

Figure 5. Increase in bacillary dysentery in Scotland over 30 years. Annual notification rates per 100,000 population, 1930–1960.

the opportunities for the spread of infection associated with poor standards of hygiene are likely to be more important than malnutrition.

PREVENTIVE MEASURES

Measures for the prevention or control of enteric infections may be aimed either at increasing the resistance of the host or at reducing the risks of exposure to infection.

Age and nutrition are essentially factors affecting the host and therefore we must consider how these two factors may be utilized, in the light of our knowledge of enteric infections, to raise host resistance. Both factors are intimately concerned in the incidence and severity of weanling diarrhea and both may operate by affecting either natural resistance or acquired immunity. Normal physiology is easily upset in early infancy, often with serious consequences to the child, and therefore normal functions must be safeguarded as much as possible during the first 6 to 12 months of life. The best safeguard against enteric infection at this age is breast feeding, and every effort must be made to encourage and facilitate this protective practice, particularly in communities where weanling diarrhea takes a heavy toll of life. Here, health education of a practical applied kind suited to the intelligence and customs of the community is likely to be the most effective preventive measure. The reasons given for early weaning must be ascertained and countered and the risks attendant on artificial feeding emphasized to both mothers and potential mothers; unfortunately, there are often strong commercial pressures to adopt some form of formula feed. When, after six to nine months, breast milk must be supplemented and gradually replaced by artificial feeding, advice on the preparation of simple and cheap formulas should be widely disseminated. The INCAP studies demonstrated that an adequate protein-calorie intake after the weaning period was effective in reducing both morbidity and mortality from diarrheal disease, whereas various environmental improvements had no beneficial effect (Table 5). Adequate nutrition ensures normal growth and function and probably raises resistance to enteric infections by maintaining healthy mucous membranes and perhaps a good supply of protective and detoxicating enzymes. The diarrheal episode in the undernourished child tends to be protracted and recurrent, compared with the short, sharp, single attack in the well fed baby. Of course, an adequate intake of food must be resumed as early as possible after the attack of diarrhea.

It is difficult to know what part acquired immunity may play in raising resistance to enteric infections in early childhood. It is unlikely to play a significant role in weanling diarrhea with its early age of attack and multiple etiologies, although it may help to reduce the clinical attack rate for shigellosis in the three to five year olds in hyperendemic areas. The same is true for older age groups in endemic cholera communities. As for artificial immunization against enteric infections, it is well known that antibody responses are poor in early infancy and, in experimental animals at least, in the presence of gross malnutrition. It is also known that attempts at prophylactic immunization of healthy adults against shigella infections have been unsuccessful, so that the prospects of artificial immunization against this specific infection are very poor. The chances of success are equally dismal in E. coli and

Table 5. *Population, Deaths by All Causes and Mortality Rates per 1000 Cohorts 5, 6 and 7. Mortality: May 1959–April/May 1963*

VILLAGE	0–5 MONTHS INCLUSIVE			6–18 MONTHS INCLUSIVE			19–36 MONTHS INCLUSIVE		
	Births	Deaths	Rate	Births	Deaths	Rate	Births	Deaths	Rate
Santa Cruz Balanya (Control)	208	32	153.8	176	17	96.6	159	4	25.2
Santa Maria Cauque (Treatment)	155	9	58.1	146	13	89.0	133	3	22.6
Santa Catarina Barahona (Feeding)	108	9	83.3	99	3	30.3	96	1	10.4

salmonella infections, with the exception of typhoid fever. The prospects are brighter in cholera provided we can improve the antigenic quality of the cholera vaccine and remember that, because young children have little or no basic immunity, a course of two doses is needed, whereas one dose may suffice in older age groups (Fig. 4).

SUMMARY

The enteric infections have their highest incidence and greatest severity in the age group from birth to five years, and both morbidity and mortality rates decline rapidly from the second year of life. Persistence in breast feeding is the most effective measure to delay the age of attack, and the maintenance of adequate protein-caloric intake after weaning will help to reduce both the incidence and severity of enteric infections. Naturally acquired immunity plays a part in raising resistance to specific infections like shigellosis and cholera in hyperendemic areas. Artificial immunization will become increasingly useful in the protection of young children against typhoid fever and cholera.

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Changing Trends in Infectious Hepatitis

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The changing trends of thought about viral hepatitis have encompassed a number of sharply divergent points of view. Attesting to the world-wide interest in it are several thousand papers written in 23 languages during the past three decades. From its earlier position as a relatively unimportant disease, it has emerged as one of the biggest unsolved problems of infectious disease in the third quarter of this century. Thrust into prominence by the large military outbreaks of World War II, it soon involved large numbers of civilians in many widely separated parts of the world. The appellative dilemma encountered in its nomenclature was solved, in part, by separating two forms of disease: infectious hepatitis caused by virus A and serum hepatitis caused by virus B. Cognizance was taken of the pandemic status of the former at meetings of the Expert Advisory Committee on Hepatitis of the World Health Organization in 1952 and again in 1963. The importance of serum hepatitis was also recognized, particularly as a cause of serious and, not infrequently, fatal disease in debilitated or elderly persons.

In the early 1940's, the definition of certain differences between infectious hepatitis, an enteric disease, and serum hepatitis, an artificially transmitted disease, was an important step in the evolution of our knowledge about these two forms of disease.[14, 15] However, the failure to propagate their causative agents in any host except man and the lack of a specific serologic test for their identification have delayed the answers to numerous questions about them and their interrelationships. Fortunately, a number of studies in volunteers conducted in this country and abroad during the past 25 years have amassed a large amount of data about these two forms of hepatitis and their causative agents. In addition, an imposing array of clinical and epidemiologic observations contributed significantly to the information about them. Under the circumstances of the somewhat laborious evolution of our knowledge, it is not unusual that changes in thinking about hepatitis should have occurred.[8] It is the purpose of this paper to review briefly the development of certain of our present concepts.

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CAUSATIVE AGENTS

Hepatitis virus A passes through bacteria-tight filters, is transmissible in series to man by oral or parenteral inoculation, and evokes homologous immunity. It survives heating to 56° C. for 30 minutes and storage in the frozen state for prolonged periods. It is present in the blood and feces of patients during the latter half of the incubation period and in the acute phase of disease when it is also present in the urine.[6]

Hepatitis virus B passes through a gradacol membrane of 52 $m\mu$ average pore diameter, indicating a size of 26 $m\mu$ or less. It is transmissible in series to man by parenteral inoculation, but its capacity to evoke homologous immunity is inconstant and actually there is little knowledge about the immune response. It survives storage at room temperature (approximately 90° F.) for six months and in the frozen state for prolonged periods. It withstands heating to 60° C. for four hours and exposure to a variety of chemicals. Heating to 60° C. for ten hours inactivates it. Viremia is present in patients during much of the long incubation period as well as in the acute phase of disease. Whether multiple strains of virus B exist is not known, although there is evidence to suggest that this may be true.[13]

Over the years of the experimental studies in hepatitis, many efforts have been made to propagate these agents in an unusually wide variety of animals and birds, embryonated eggs, and cultures of cells of animal and human origin. Although most of these attempts were regarded as failures, a gradually increasing number of claims for success have appeared, particularly during the past decade when tissue culture has become the medium most commonly used. At least a score of so-called "candidate viruses" have been isolated by these various techniques but, up to the present, none of them has been unequivocally proved to be causatively related to viral hepatitis. In addition to a number of animal viruses inherent in the test animals used and unrelated to human hepatitis, a number of known human viruses, including strains of ECHO and adenoviruses, Coxsackie virus, herpes simplex virus, myxovirus, REO virus, and cytomegalic inclusion virus, have been isolated in testing specimens of blood, feces, and pharyngeal washings of patients with hepatitis. Their association with hepatitis has been regarded as fortuitous. Of some interest is the frequency of recovery of adenoviruses under these circumstances, and the question has been raised whether they might be implicated in conjunction with other as yet undefined "helper viruses" as causative agents of human hepatitis. As yet, there is no evidence available to support such a concept.[4]

During the past 25 years, numerous attempts were also made to transmit hepatitis to nonhuman primates by inoculation of serum and/or feces obtained from patients with hepatitis or with certain of the "candidate viruses" isolated from such patients. All but a few of these experiments were judged unsuccessful, and in those studies in which success was claimed, the positive results have not, as yet, been uniformly reproducible. However, this promising work is continuing, and it is important to point out that the great efforts currently being put into such studies were justifiably prompted by the report of Hillis[9] in 1961 of an outbreak of hepatitis among handlers of chimpanzees newly arrived in the United States. Since then, the Communicable Disease Center in Atlanta, Georgia, has assembled data on 102 cases of hepatitis in persons who had close contact with chimpanzees, monkeys, or gorillas three to six weeks before the onset of disease. Most of them were chimpanzee associated, and it is of interest that the attack rate of infectious hepatitis is significantly higher among chimpanzee handlers than in the general population.[1] These findings suggest that nonhuman primates may be infected by exposure to virus after trapping, either in Africa while awaiting shipment or soon after arrival in this country. Without evident clinical disease, they may excrete virus and be infectious for persons in close contact with them. These epidemiologic observations and the occasional isolated claim for successful experimental transmission of hepatitis to nonhuman primates provide hope that some nonhuman primate may be found to be uniformly susceptible to hepatitis virus.[4]

PATHOGENESIS

Little is known about the pathogenesis of viral hepatitis. The lesions in the liver are generally ascribed to the direct impact of virus on hepatic cells, but there is as yet no positive evidence for this, and the variably sized particles visualized by electron microscopy in hepatic cells of patients with acute hepatitis have not been proved to represent hepatitis viruses.

The viremia in the alimentary phase of infectious hepatitis and the prolonged viremia in serum hepatitis before any evidence of hepatic damage is present have raised the question whether any eventually occurring hepatic damage might be due to some form of antigen-antibody interaction. This was suggested early by Gear[5] during serologic studies with serum hepatitis in which certain hyperergic manifestations such as itching, urticaria, and arthralgia not uncommonly occurred just before the appearance of jaundice.

More recently, there has been renewed interest in the possibility that the development of chronic hepatitis is potentiated by autoimmune mechanisms, and a number of studies using fluorescence microscopy and various serologic techniques have furnished data revealing that chronic hepatitis may indeed flourish in a biologic environment containing autoantibodies.[16] However, they have not, as yet, been proved to have a causative role.

EPIDEMIOLOGY

Viral hepatitis is not a reportable disease in large areas of the world. Because of its contemporary importance, it has been made notifiable, but relatively recently, in the United States, Canada, Australia, New Zealand, Japan, Israel, and certain countries of Europe. Notable exceptions are Sweden and Denmark, pioneers in the recognition of both forms of the disease. From the latter country are available epidemiologic data that furnish the longest and most accurate uninterrupted history of experience with infectious hepatitis during the past 38 years. Two major epidemics occurred in Denmark during this time, the first reaching its peak in 1933 and the second in 1943. Since then, the morbidity of hepatitis has declined steadily, with few exceptions, to 22.1 per 100,000 in 1964, the lowest annual rate reported thus far in Denmark. Similar patterns have been recorded for other northern countries, including Finland, Norway, Canada, and the Netherlands, during the past decade. Compulsory reporting in Hungary and Czechoslovakia has revealed pandemic conditions during this period, while

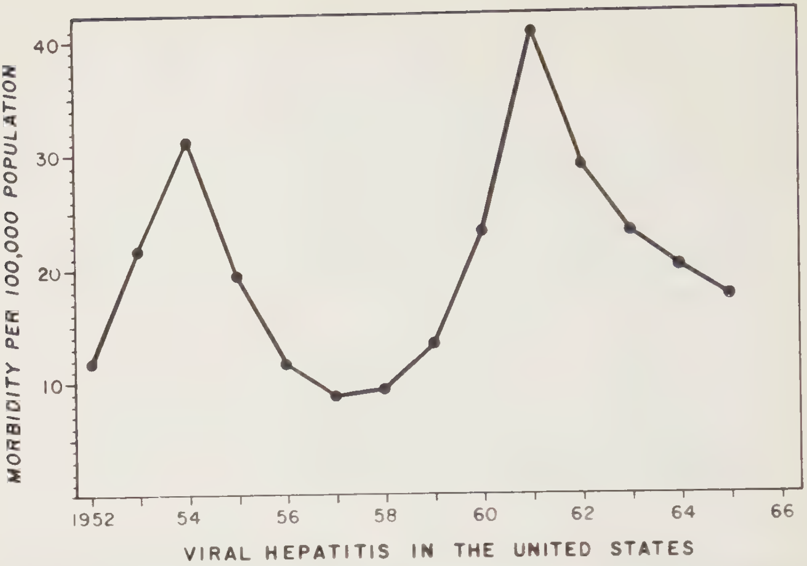

Figure 1. The data used in preparing this chart were taken from Communicable Disease Center Hepatitis Surveillance Reports No. 4, March 21, 1961; No. 15, May 13, 1963; and No. 25, March 31, 1966.

in Greece and Italy the rates have been low, suggesting that the available figures may reflect the presence of a milder disease that escapes diagnosis or possibly less accurate notification.[11]

In the United States, our major contemporary experience with viral hepatitis began with the rude confrontation with homologous serum jaundice early in 1942 when it appeared in large numbers of troops who had received yellow fever vaccine stabilized with human serum. Nor was this to be our sole experience with hepatitis, for our troops next encountered the epidemic form of the disease, along with Allied and Axis forces, in North Africa, Sicily, Italy, France, and Germany. Approximately 200,000 American cases were admitted to military hospitals between 1942 and 1945, and the disease has continued to involve our military personnel in varying degrees in different parts of the world up to the present time.

Civilians in this country have also participated in the epidemic experiences of the past 25 years. Despite its obvious importance, viral hepatitis was not made universally reportable in the United States until 1952. From that time through 1965, approximately 500,000 civilian cases have been reported. Since patients with jaundice make up the bulk of these, it is evident that the morbidity has doubtless been far greater than one might suspect from the data available. In addition, it is probably still true that even the reporting of hepatitis with jaundice is not complete. The importance of the disease stimulated the formation of the Hepatitis Surveillance Unit by the U.S. Public Health Service in 1960, and from the reports of this Unit a great deal of valuable epidemiologic information has become available. Two epidemics have occurred, with peaks in 1954 and 1961, constituting a seven-year cycle similar to the six- to ten-year cycles commonly described in other countries (Fig. 1). From the peak year of 1954, the incidence of hepatitis declined progressively for four years, after which a reversal of trend occurred, with a rapid build-up to the peak year of 1961. This was followed by another progressive decline for the five years to 1966. If a similar pattern repeats itself, it would not be surprising to have again a reversal of trend, with an increasing incidence reaching its peak in 1969.[3] That the pattern of incidence of viral hepatitis need not follow the long-term (six to ten years) cycles seen in Europe and the United States is attested by the experience in Israel[2] where the epidemiologic pattern among civilians has been characterized by a two-year cycle, with alternate years of high and low incidence (Fig. 2).

Although viral hepatitis goes unreported in many places in the world, the available evidence, obtained largely from northern countries, would suggest that its seasonal distribution follows a pattern of increase in the autumn and early winter, with decline in the spring and summer. Whether this occurs in areas of poor sanitation and in all climates is not known. However, data obtained from Israel during the past 15 years indicate that there in a warm climate a similar seasonal distribution occurs.

Over the years, the accumulated evidence from experiments in volunteers and epidemiologic data has demonstrated that infectious hepatitis is spread by the fecal-oral route, largely by person-to-person contact. The role of the carrier and the patient with minimal evidence of disease in the natural history of infectious hepatitis is well established. The prevalence of anicteric hepatitis or unrecognized infections particularly among children puts adults closely associated with them at risk and constitutes an important way of spread in civilian life. In addition, common-source outbreaks implicating foodstuffs and water have been well documented, and indeed the solution of certain of them has been a triumph for the epidemiologist. Infected food handlers are doubtless the cause of some food-borne outbreaks, and the importance

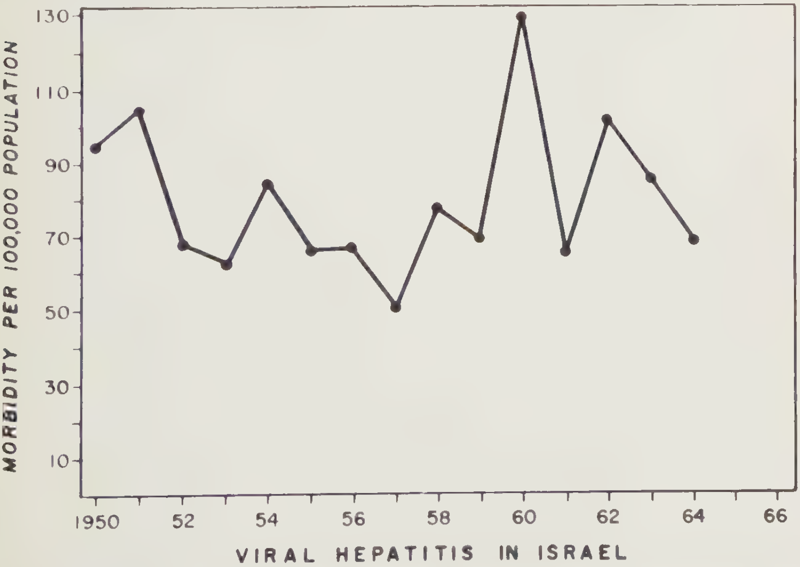

Figure 2. The data used in preparing this chart were taken from Communicable Disease Center Surveillance Report No. 25, March 31, 1966. Rates for Jewish population only in 1950–1953.

of raw clams and oysters from polluted waters as a source of infection has been emphasized.[1]

Little is known about the epidemiology of serum hepatitis in regard to its incidence or geographic distribution, although it has been described in several widely separated parts of the world. With the exception of common-source outbreaks, it is difficult to distinguish between it and infectious hepatitis, and little effort is made to do so in reporting to public health authorities. Common-source outbreaks occur when groups of persons are infected (*a*) with an aliquot of a pool of material containing virus, such as plasma, or (*b*) by parenteral inoculations in places where instruments are inadequately sterilized. The former type has diminished sharply in incidence in this country during the past ten years. The latter probably accounts for more spread of hepatitis than is suspected; however, in this country it would appear that transfusions of whole blood are a more important way of spread at present.

All age groups are susceptible to serum hepatitis, and it is not known whether this is due to (*a*) the existence of multiple strains of virus, (*b*) failure of virus to evoke sufficient immune response, or (*c*) inadequate exposure because of artificial transmission. In addition to these mysteries, there is also little knowledge about the epidemiologic relationship of infectious hepatitis and serum hepatitis. That the two may coexist in the same geographic areas or even in sharply localized areas, as clinics, is well known, and the possibility of transmitting two immunologically distinct viruses with long and short incubation periods obfuscates the situation even more.

RELATIONSHIP OF INFECTIOUS HEPATITIS TO SERUM HEPATITIS

The relationship between infectious hepatitis and serum hepatitis and their causative viruses is poorly understood. They appear to be immunologically distinct. The recognized clinical patterns of both diseases are similar except that in serum hepatitis the incubation period is much longer and the onset of disease more insidious and associated with little fever. Although jaundice is generally regarded as an important distinguishing sign of viral hepatitis, its frequency of occurrence is highly variable.

The clinical course of infections with hepatitis viruses comprises a wide spectrum, with extremes ranging from asymptomatic infection without evidence of hepatic dysfunction to fatal illness associated with severe jaundice.[7] The latter is uncommonly encountered, since the overall mortality of hepatitis is low. The former is rarely defined, since its recognition depends on studies of volunteers or of donors of blood who are presumed to have been carriers of hepatitis virus. Between these widely spaced extremes lies the great bulk of infections that come to clinical awareness, progressing in severity from asymptomatic disease with mild hepatic dysfunction to clinically recognizable hepatitis with or without jaundice. Our concept of the frequency of these variations of disease as well as the true incidence of infection with hepatitis viruses is sharply limited by the lack of specific methods to identify them or to measure immunologic experience with them.

Infectious hepatitis is an acute enteric infection with generalized systemic involvement. Its course may be modified by the administration of normal immune globulin during the incubation period. Epidemiologic, clinical, and pathologic evidence early focused attention on the alimentary phase of disease, and experiments in volunteers proved that virus A was excreted in the feces during the acute phase of disease and was transmissible to volunteers by feeding. Subsequent studies in volunteers revealed the presence of virus A in the blood and feces of children in the incubation period of experimentally transmitted hepatitis when there was no evidence of clinical disease or hepatic dysfunction two to three weeks before the appearance of jaundice.[10] The importance of this initial alimentary phase in the natural history of epidemic hepatitis is recognized. That it may at times constitute the complete expression of disease without demonstrable hepatic involvement is also possible. The relative frequency of hepatitis without jaundice in young children supports this concept.

Serum hepatitis is clinically similar to infectious hepatitis and its severity comparable when it occurs in otherwise healthy persons of similar ages. However, it may be much more severe and associated with a greater mortality in older, physically depleted persons in whom it most commonly occurs at present. Preliminary studies suggest that its course may also be modified by the administration of normal immune globulin during the incubation period. Although gastrointestinal complaints and pathologic findings at autopsy are similar to those of the epidemic disease, there is no evidence to support the existence of a true alimentary phase in serum hepatitis. Virus has not been found in the feces, nor has the disease been produced in volunteers by feeding infectious materials (serum). Viremia has been shown to persist for prolonged periods in asymptomatic persons, and virus has been recovered from the blood of experimentally infected volunteers when they had no evidence of clinical disease nor abnormalities of hepatic function 87, 60 and 16 days before the onset of clinical hepatitis. This prolonged equilibration between virus and host in serum hepatitis is as poorly understood as the forces that terminate it, making clinical disease possible. How often the termination of this relationship is in favor of the host and, therefore, unassociated with any evidence of clinical disease is unknown, but it probably occurs more often than suspected. The importance of the asymptomatic carrier in the natural history of serum hepatitis is recognized.

The differences between the natural histories of these two diseases and their ways of transmission as well as the immunologic differences between their causative viruses have intrigued those working with them over the years. That serum hepatitis depends on parenteral penetration for survival is difficult to accept, and it would seem likely that some less tenuous way exists. In a small number of experiments in volunteers, it has been shown that virus A, but not virus B, when inoculated parenterally is excreted in the feces. That these results do not conclusively furnish evidence that virus B is never excreted in the feces is suggested by the rare occurrence of hepatitis in wives of soldiers with serum hepatitis and the description of an outbreak of serum hepatitis in which contact cases seemed to have occurred.[12] Since this situation is not settled, a plausible and less precarious way of biologic survival might be based on the emergence of new strains of virus in man. Although the period of infectivity of the blood and feces of patients with infectious hepatitis is usually regarded as lasting four to five weeks, there are notable exceptions to this, and infectivity has been proved to last several months. Thus, virus A conceivably might undergo alterations during such a prolonged residence in the body, emerging with properties now believed to be characteristic of virus B. Such changes need not be complete, and the maintenance by certain strains of such previously characteristic properties as capacity for excretion in the feces after parenteral inoculation could account for the occasional appearance of contact cases in serum hepatitis. In such a fashion, biologic survival would be implemented but transmission might still depend almost completely on parenteral inoculation.[8]

SUMMARY

During the early 1940's, viral hepatitis emerged from relative obscurity and was separated into two clinically similar but immunologically distinct entities: infectious hepatitis (caused by virus A) and serum hepatitis (caused by virus B). The latter produced the first great iatrogenic epidemic in military forces. The former also quickly involved the military in large outbreaks, and during the next 25 years became pandemic among civilians. Infectious hepatitis is an enteric disease, spread by the fecal-oral route largely by person-to-person contact. Its severity may be modified by the administration of normal immune globulin. Serum hepatitis is transmitted by the parenteral inoculation of infected human blood or certain of its products, and preliminary studies suggest that its severity may also be modified by the administration of normal immune globulin.

Studies in volunteers and clinical and epidemiologic observations have provided the available information concerning these two forms of hepatitis and their causative agents. Their interrelationships remain obscure and doubtless will continue so until suitable techniques are available for the propagation of human hepatitis viruses in the laboratory.

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The Impact of Vector-Borne Viral Diseases in the Middle Atlantic States

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Approximately 200 types of arboviruses have been recognized throughout the world. Of this large number of viruses, four types are presently considered important causes of encephalitis in the United States, namely, eastern encephalitis virus, western encephalitis virus, St. Louis encephalitis virus, and the California group of viruses. Outbreaks of encephalitis due to two of these agents, eastern and St. Louis encephalitis viruses, are known to have occurred in the Middle Atlantic States. This paper will outline briefly some aspects of the epidemiology and ecology of these arboviruses as found in this area. Much of the data presented here is excerpted from several papers, awaiting publication, by a large group of investigators at the New Jersey State Department of Health.

EASTERN AND WESTERN ENCEPHALITIS

We will commence our discussion of arboviruses with the eastern and western encephalitis viruses, which can be discussed together because their ecology seems to be similar in the eastern part of the United States.

Western encephalitis (WE) virus was first isolated in California by Meyer and co-workers in 1930.[27] Numerous outbreaks of WE, involving both humans and horses, have been recognized in subsequent years. All these outbreaks have occurred in the western portion of the United States and Canada. Studies[19, 31] have amply documented that the epi-

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Table 1. *Distribution by Age and Sex of Cases of Eastern Encephalitis in New Jersey in 1959*

AGE (years)	MALE	FEMALE	TOTAL
0– 4	6	5	11
5–14	7	4	11
15–24	1	0	1
25–34	0	1	1
35–44	0	0	0
45–54	0	0	0
55–64	1	3	4
65+	2	2	4
TOTAL	17	15	32

demic mosquito vector is Culex tarsalis, a species prevalent in the western part of the continent but not found on the eastern seaboard. These studies have also demonstrated that Culex tarsalis is probably the epizootic and enzootic vector of WE in the West. This dual role of Culex tarsalis, as both an epidemic and epizootic vector, has led to a tendency among investigators to apply the concept of a unitary vector to other situations. On the basis of recent studies by our group and others, we do not feel that this concept is valid.

The first isolation of eastern encephalitis (EE) virus was made in New Jersey by Ten Broeck and Merrill,[33] who isolated this virus from horse brains and serologically differentiated it from the WE virus. Numerous outbreaks of equine illness and death have been recorded over the years in New Jersey. EE virus has also been found to be the cause of an epizootic encephalitis in pheasants.[36]

The first recorded human outbreak of EE occurred in Massachusetts in 1938, and subsequently smaller outbreaks occurred there in 1955 and 1956.[8] Outbreaks of EE also occurred in Louisiana in 1947[23] and in the Dominican Republic in the winter of 1948–1949.[5] Additional isolated human cases of EE have been reported over the years. In all these outbreaks of EE, the number of human cases has been relatively small, the largest number being 27 authenticated cases in Massachusetts in 1938. The mortality, however, has been very high; two-thirds of the patients died during the acute illness.

EE virus was first isolated in New Jersey; equine and pheasant outbreaks had occurred over the years, and epizootic activity of EE virus had been more consistently and regularly confirmed in New Jersey than elsewhere, but no human cases of EE were recognized in New Jersey before 1959. Early in 1959, two of the authors (M.G. and O.S.) began a study to determine whether unrecognized cases of EE were occurring in New Jersey. That very year, human cases of EE were found in the state.

The detailed description of this outbreak has been presented by Goldfield and Sussman.[11] In brief, 31 human cases of EE were identified in New Jersey in 1959. In all 31 cases considered to be EE there was either serologic or virologic evidence of EE infection,[13, 32] or pathologic evidence of encephalitis consistent with that found in proved cases of EE. Twenty-one of the 31 human cases were fatal. The human outbreak began the last week in August, reached a peak in the first week of September, and lasted through the second week of October. The age and sex distribution of the cases revealed a paucity of cases in the 15 to 55 year old age groups (Table 1). All the human cases occurred within 10 miles of the coastline. A similar situation of epidemic involvement with EE in proximity to the seacoast has been found in the other outbreaks of EE.

Before 1959, it was generally believed that inapparent infection of man with EE rarely occurred, despite a few scattered reports of EE serologic activity in humans not known to have had overt encephalitis. It was held that, once infected, man almost invariably developed severe encephalitis.

During the course of the 1959 EE epidemic in New Jersey, it was decided to study the possibility that inapparent EE infection occurred with measurable frequency. Volunteer bleeding clinics were held in selected communities in the epidemic area immediately following the outbreak, and again in 1961.

As shown in Table 2, 2.1 per cent of the persons tested in communities in the epidemic area showed evidence of recent EE infection, as demonstrated by complement-fixing reactivity to EE and confirmed by mouse neutralization tests.[16] The age distribution of those with recent infection by EE virus was not significantly different among the various age groups. Thus, this study showed that there was not a decreased exposure or susceptibility to infection by EE virus in the 15 to 54 year old age groups, but rather a decreased likelihood of developing overt encephalitis following infection. Calculation of the inapparent infection to disease ratio yielded a figure of 23 inapparent infections for each case of overt encephalitis.[17] Many of the persons with inapparent infection had a history of a minor illness during the epidemic period (56 per cent as compared to 11 per cent of the overall study population).

In addition to the demonstration of recent inapparent infections, some CF-negative residents of the epidemic area were found to possess EE hemagglutination inhibition and neutralizing antibody.[14] There was no greater incidence of minor illness in this group than in the overall surveyed population, and none of this group had resided in the area less than seven years before 1959. The likelihood of possessing such a serologic pattern increased with increasing duration of residence in the area (Table 3). This serologic pattern most probably reflects EE infection in the more distant past, and thus, the residents of the area were repeatedly exposed to EE infection over the years. In other words, there were probably repeated, unrecognized outbreaks of EE in the epidemic area for at least as long as the lifetime of the present residents.

As a consequence of the EE outbreak of 1959, a large-scale ecologic study of EE in New Jersey was initiated by two of the authors (M. G. and O. S.). The study presently consists of the maintenance of four study sites, three at shore areas and one inland in northern New Jersey in an area in which no evidence of previous human EE infection could be found. At these study sites, birds, animals, and mosquitoes are continually caught and tested for EE and WE viruses, and neutralizing antibody determinations for EE and WE are performed on appropriate specimens.

Table 2. *Incidence of Recent EE Infection in Residents of the Shore Area of New Jersey, 1959 and 1961 Bleedings*

AGE (years)	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
0– 4	100	2	2.0
5–14	647	17	2.6
15–24	192	3	1.6
25–34	292	8	2.7
35–44	303	5	1.7
45–54	276	4	1.4
55+	260	5	1.9
TOTAL	2070	44	(2.1)

Table 3. *Incidence of Past EE Infection as a Function of Duration of Residence in Persons from Four Selected Communities of the Shore Area of New Jersey*

DURATION OF RESIDENCE*	NUMBER TESTED	NUMBER NEUT. POSITIVE	PER CENT NEUT. POSITIVE
0– 4	412	0	0
5–14	642	7	1.1
15–24	202	3	1.5
25–34	131	8	6.1
35–44	96	4	4.2
45–54	70	5	7.1
55–64	28	2	7.1
65+	25	3	12.0
TOTAL	1,606	32	(2.0)

*As of 1959.

These ecologic studies are being conducted by a large group of investigators at the New Jersey State Department of Health, and will be reported in a series of papers by these investigators. Some of the results have already been briefly summarized.[10] A detailed description of the ecologic studies is beyond the scope of this presentation, but some conclusions drawn from the studies are as follows:

1. Epizootic activity of EE and WE viruses probably occurs in a large area of New Jersey and is not limited geographically to the shore area, as is epidemic EE activity. During the period of our studies, WE infection has been predominant in some years but in others most of the activity has been EE.

2. Contrary to the general belief at the onset of these studies that birds were the primary hosts of EE and WE, it now appears that the primary hosts may be some as yet unknown species of nonavian vertebrates. Numerous isolations of these viruses have been made from many species of mammals, reptiles, and amphibians, and neutralizing antibodies to EE and WE have been found in almost all of these species. These virus isolations have been made throughout the year, particularly in the colder months.

3. As a corollary to the previous point, the viruses of EE and WE are known to be present the year round in New Jersey and it is not necessary to postulate an annual reintroduction each year by migratory birds, as was previously thought. It is our hypothesis that birds are infected after arrival in New Jersey, and that the vectors transmitting the viruses from nonavian vertebrates to birds may be a variety of Culex species of mosquitoes.

4. Many investigators have stressed the importance of Culiseta melanura, a primarily avian-feeding, fresh-water-marsh mosquito, in the transmission of EE, mainly because of the large number of isolates of EE obtained from this species. It is now considered probable that Culiseta melanura is important only in the bird to bird transmission of both EE and WE. Such transmission has great importance in the development of an avian epizootic of EE, which is probably a necessary precursor of an epidemic. However, except for possibly occasional scattered cases of EE, Culiseta melanura is not considered by us to be the vector in the epidemic transmission of EE to humans in the Middle Atlantic area.

5. Because of the geographic localization of epidemic EE to areas in proximity to the seacoast, Aedes sollicitans, a salt-marsh mosquito that is an avid human feeder, has been hypothesized as the epidemic vector of EE. All our studies to date have supported this hypothesis.

ST. LOUIS ENCEPHALITIS

St. Louis encephalitis (SLE) was first recognized as an entity during a severe outbreak in Missouri and surrounding states in 1933.[21] SLE accounts for more cases than any other arbovirus encephalitis in the United States, although the mortality rate and incidence of severe sequelae are not nearly as high as those of EE.

Epidemics of SLE fall into two epidemiologic patterns. One pattern is found essentially in the Far West. Almost all such epidemics have been mixed outbreaks of WE and SLE and have occurred mainly in rural areas. The epidemic and epizootic vector of SLE, as well as of WE, in such outbreaks has been shown to be Culex tarsalis.[19, 31]

The original St. Louis epidemic and numerous subsequent epidemics in the Middle West have occurred in a more urban locality. These outbreaks have been noteworthy in the tendency for older persons to be ill. In these urban SLE outbreaks, the epidemic vector has been mosquitoes of the Culex pipiens-quinquefasciatus complex, mosquitoes generally associated with the home and urban environment.

Although numerous outbreaks of SLE have been reported in the Middle and Far West, no outbreaks of SLE had ever been reported in the northeastern United States before 1964. The only place on the eastern seaboard where SLE had occurred was in Florida, where the epidemic vector was found to be Culex nigripalpus, an essentially tropical mosquito.[3]

The New Jersey State Department of Health maintains an active program of surveillance of viral central nervous system disease, in part as a concomitant of the ecologic studies noted previously. In addition to the usual reporting procedures, cases came to our attention through the use of our virology laboratory, and through our direct contact with physicians, pathologists, and hospitals throughout the state. As a result of these surveillance procedures, a concentration of cases of suspected viral central nervous system disease was recognized in Camden and Burlington Counties, adjacent to Philadelphia, in late September, 1964. Despite the fact that SLE had never been known to have occurred in the Middle Atlantic States, the epidemiology of these cases suggested an outbreak of SLE.[1] Rapid laboratory confirmation was obtained that the outbreak was indeed SLE.

The investigation of this outbreak was extended to Pennsylvania because the Delaware River was not considered to be an effective barrier to spread of the virus. Unfortunately, a variety of circumstances prevented as complete a search for SLE cases in Pennsylvania as was made in New Jersey, so that the data for the two states are not fully comparable.

All patients considered to have SLE in this epidemic had a clinical history of a central nervous system illness and serologic evidence of SLE infection.[15] One hundred and seventeen patients with SLE were discovered, 97 in New Jersey and 20 in Pennsylvania. Two-thirds of the patients were over 45 years of age and two-thirds were female (Table 4). The cases occurred from early August to mid October, with the peak in

Table 4. *Age and Sex Distribution of Cases of St. Louis Encephalitis in New Jersey and Pennsylvania in 1964*

AGE (years)	MALE	FEMALE	TOTAL
0– 4	2	0	2
5–14	1	2	3
15–24	4	3	7
25–34	4	7	11
35–44	7	11	18
45–54	6	18	24
55–64	3	13	16
65+	12	24	36
TOTAL	39	78	117

September. All of the patients were probably infected within 10 miles of the Delaware River. Mosquito studies suggested that, as with other urban outbreaks, Culex pipiens mosquitoes were the epidemic vector.[12]

Since SLE or other Group B arbovirus outbreaks had not been known to have occurred in the epidemic area during the lifetime of the present residents, it was thought to be a unique opportunity to perform a serum survey. The purpose of this survey was to determine whether the age and sex incidence of the inapparent infections was the same as that among the cases, and also to establish whether there was evidence of prior Group B arbovirus infections in the area.[9]

Bleeding clinics were held in three communities in the epidemic area. In addition, Health Department personnel went house to house in the communities to obtain additional bloods.

A total of 7851 usable sera were obtained in this survey, making this the largest serologic survey for arboviruses ever conducted in the United States. These sera were tested in both complement fixation and hemagglutination inhibition tests against SLE, and only positive results that were confirmed by mouse neutralization tests were accepted as instances of recent SLE infection. In addition, a group of CF- and HI-negative sera were picked randomly for a neutralization test as a determination of past infection. A total of 1892 mouse neutralization tests were performed, 1229 of these on CF- and HI-negative sera.

A more detailed analysis could be carried out on the permanent residents of the three communities of the clinics, as demographic data could be applied to this group. A total of 6805 useable sera were obtained from these permanent residents, representing one-tenth of the population of these communities. An overall infection rate of 2.1 per cent was found, varying slightly among the communities. Calculation of the inapparent infection to disease ratio for the three study communities reveals a ratio of 54:1.

The unequal age and sex distribution of the patients with SLE raised the question, as in the EE outbreak, of whether the distribution was due to a difference in infection rate or to a difference in the clinical response to infection. The survey showed no significant difference in the infection rate for SLE among the various age groups (Table 5) and no significant difference in the infection rate by sex. These findings are at variance with the original findings of some recent studies.[28, 29] in which neutralization tests were not initially performed. In these studies, a rising infection rate with age was noted. However, later work in the same areas[2, 22, 26] showed that much of the reactivity in the older persons was related to prior infection by another Group B arbovirus, namely dengue, and that there was no real difference among the different age groups in respect to SLE.

The serum survey revealed no evidence of past infection with SLE in the communities studied. However, cases of SLE continued to occur in the epidemic area in 1965, two in New Jersey and one in Pennsylvania. Such a finding raises the possibility that SLE may occur again in this area and stresses the need for continued vigilance.

One of the main concepts that we have tried to foster has been that, although epidemic activity of the arboviruses may be directly related to epizootic activity, epizootic and enzootic activity may be occurring without any concomitant epidemic activity. This has been discussed previously in relation to EE and WE; epizootic and enzootic activity of these viruses has been shown to occur without any evidence of epidemic activity. It is our feeling that a similar situation may exist with SLE.

The only large-scale enzootic studies that have been reported on SLE have been in the Far West, particularly in Kern County, California.[31] In this situation, Culex tarsalis is probably both the epidemic and epizootic vector, and the findings in these studies are not necessarily applicable to the urban-suburban SLE situation, where the Culex pipien-quinquefasciatus complex of mosquitoes is the epidemic vector. In such a situation, epizootic activity may occur over much wider areas than those involved in an epidemic. Our ecologic studies of EE and WE offered the opportunity to study the enzootic occurrence of SLE in an area remote from an epidemic area both at the time of an epidemic and in the period before and after an epidemic. In addition to providing information on possible independent enzootic SLE activity, such a study might also provide information about the apparent de novo appearance of SLE in the Middle Atlantic States in 1964.

There has been much speculation regarding the mechanisms by which SLE virus is disseminated over large geographic areas and the reasons for occurrence of human outbreaks in diverse places at differ-

Table 5. *Recent Inapparent Infection Rates Found in the St. Louis Encephalitis Serum Survey in New Jersey in 1964 in the Communities of Collingswood, Maple Shade, and East Camden**

AGE (years)	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
0– 4	215	7	3.3
5–14	1800	35	1.9
15–24	882	14	1.6
25–34	769	13	1.7
35–44	1255	31	2.5
45–54	909	26	2.9
55–64	536	9	1.7
65+	437	7	1.6
TOTAL	6805†	142	(2.1)

*Permanent residents.
†Includes two persons of unknown age.

ent times. Generally speaking, two hypotheses have been propounded and widely discussed:

1. SLE virus may survive for many years in certain localities, and when conditions are right, an epizootic is generated among wild birds by Culex pipiens mosquitoes and is followed by the occurrence of an epidemic. This hypothesis might be called the "recrudescence" hypothesis.

2. SLE virus may be transported over long distances by migratory birds, and when such an introduction is made into an area, an epizootic among birds mediated by Culex pipiens mosquitoes may result in a human outbreak. This hypothesis, which we may call the "island" hypothesis, is presently most widely accepted. Thus it has been postulated that SLE was transported in 1964 to such distinct and separate foci as Texas, Illinois, Kentucky, Tennessee, Indiana, Colorado, and metropolitan Philadelphia.

We would like to propose another hypothesis regarding the spread of SLE into the Middle Atlantic area. It can be postulated that a solid epizootic wave of SLE swept across a large part of the northeastern United States in 1964, or in the immediately preceding years, and that the isolated epidemic resulted from the development of a secondary urban bird-Culex pipiens cycle in the specific locality.

As previously mentioned, the four study sites of our arbovirus studies are along the shore and in the northern part of New Jersey, all in areas at some distance from the site of the 1964 epidemic. The collections from these sites would provide a source of wildlife material continually collected away from an epidemic area. Unfortunately, for economic reasons, most of the testing of this material has been done in wet chicks, a system sensitive to EE and WE (the original purpose of the study) but not useful for the isolation and serologic testing for SLE. Adequate isolation procedures for SLE require the use of suckling mice, a vastly more expensive and time-consuming procedure. On a somewhat limited scale, we have begun some testing for SLE from our wildlife collections.[12]

These studies are still incomplete, and once again, any detailed discussion of them is beyond the scope of this presentation. We can say, however, that neutralizing antibody to SLE has been found in nonavian vertebrates collected at all four of our study sites as well as in animal bloods brought to our laboratory from other areas of the state. These findings are suggestive that SLE activity is widespread throughout New Jersey, although we cannot be certain that this activity is not due to some other related Group B arbovirus.

A more secure indicator of SLE activity would be the isolation of SLE virus. With this in mind, we have been retesting our mosquito pool collections from our study areas in suckling mice. To date, most of the collections from 1964 and 1965 have been tested. Three isolations of SLE have been made, one from a 1964 pool and two from 1965 pools. All of these mosquito pools have been Aedes sollicitans mosquitoes collected at shore areas. Thus, we have shown SLE activity in areas away from the epidemic area, and, what is somewhat disturbing, this activity has been found in a mosquito species that is an avid human feeder and the chief pest mosquito in New Jersey.

CALIFORNIA ENCEPHALITIS GROUP

California encephalitis virus, or, more correctly, the California encephalitis group of viruses, have not as yet occasioned much concern in our area since they have not thus far been found to cause human illness in the Middle Atlantic States.

California viruses were first isolated in 1943 in Kern County, California, from three mosquito pools.[20] Three cases of encephalitis in California at that time were thought probably due to California virus.[18] Following the initial isolations, the virus seemed to disappear. Despite intensive arbovirus studies being conducted in California, the virus was not isolated again in that state until 1963.[21] The next isolation after 1944 occurred in 1948 in North Dakota.[20] This is the so-called trivittatus virus, being isolated from Aedes trivittatus. For the next 10 years, no California virus was isolated in the United States. In 1958, the San Antonio strain was isolated in Texas. In the next few years, scattered isolations of California virus occurred around the country. Viruses of the California encephalitis group have also been isolated in many other parts of the world.[21]

Since 1963, large numbers of isolations of California group viruses have been made. In Wisconsin, both cases of encephalitis and inapparent infections have been discovered,[34] and a fatal case of encephalitis occurring in 1960 was retrospectively found to have been caused by California virus.[35] The virus strain isolated from this case, the so-called LaCrosse strain, has been considered rather closely related to strains causing many of the subsequent cases of California encephalitis discovered in the United States. In 1964 and 1965, what might be called an outbreak of California encephalitis occurred, with cases of encephalitis due to California virus found scattered in many parts of the Midwest, particularly Ohio, Indiana, and Wisconsin.[6,7] In the past two years, cases of California virus encephalitis have been found in Florida[30] and North Carolina,[7] and numerous isolations of different strains of the virus have been made in Florida.[25] California viruses are now well established as a significant cause of encephalitis in the United States.

Obviously, since large numbers of isolations and serologic identifications of California viruses have been made only since 1963, not much can be stated at this time concerning the epidemiology and ecology of these viruses. However, certain preliminary observations can be made:

1. Almost all of the recorded cases of California encephalitis have occurred in children or adolescents.
2. The case fatality rate appears low; most of the patients recover.
3. Unlike the other arboviruses already discussed, birds do not appear to be an important host of the California viruses. It has been almost impossible to show infection in birds, both naturally and experimentally.[21] Most of the potential host isolations of California viruses have been from mammals.
4. Most of the mosquito isolations of California viruses have been from Aedes species. Some tick isolations have also been made. A primary cycle involving small mammalian hosts and primarily Aedes species of mosquitoes has been suggested.[21]

In any discussion of California viruses, it is important to point out that there are significant serologic differences among the different California strains. These differences are important from both a taxonomic and diagnostic viewpoint. With many arboviruses, such differences would lead to the naming of new arboviruses within a group, and it is probably best to view the California viruses as a group of closely related arboviruses. These differences among the California group viruses are particularly important in serologic studies, because in certain tests it is important to use the proper strain of virus, and one does not always know the appropriate strain for any particular place or time.

The testing of the mosquito pools in suckling mice that we have been doing is also a method of isolating California viruses. To date, one isolate of California virus had been obtained from a pool of Aedes sollicitans mosquitoes collected in 1965. Characterization of this isolate is now in progress. In addition, we have been informed that California viruses were isolated from mosquito pools collected in New Jersey in 1960.[4] The finding of California virus in Aedes sollicitans, the chief human pest mosquito on the New Jersey shore, raises the possibility of human infection in our area, and it is probable that unrecognized California virus encephalitis has occurred. Both prospective and retrospective studies are being conducted to find such human infection and illness if it exists.

SUMMARY

The ecologic studies in New Jersey have demonstrated widespread occurrence of EE and WE viruses in our area throughout the year. An epidemic of EE was recognized in the shore area in 1959 and serologic studies suggested the periodic recurrence of epidemics of EE in this area. An epidemic of SLE occurred in the metropolitan Philadelphia area in 1964 with additional cases the following year. Ecologic studies have suggested the widespread dissemination of SLE virus in New Jersey and possibly in the whole Middle Atlantic area. Viruses of the California encephalitis group have also been isolated from mosquitoes in New Jersey. There is every reason to believe that outbreaks of EE and SLE will recur in our area and that human cases of California encephalitis will be found.

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Immunoprophylaxis of Arthropod-Borne Virus Diseases

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Vaccines and antisera for the protection of man against arthropod-borne virus diseases have been under study and development intermittently since at least the early 1930's. In this country today, however, the 17D yellow fever vaccine is the only vaccine for protection against an arbovirus infection that is licensed for distribution and use in human beings.

I have chosen to consider arboviruses generally rather than to restrict this paper to those now endemic in the United States because the problem is no longer solely a local one.

First, with our modern massive and rapid international air transportation system, viral agents from other parts of the world can be introduced into this country, through the transport of either infected vectors or people incubating an infection. Indeed, intensive prophylactic vector control measures are now being carried out in the vicinity of some major international airports. During the 1963–1964 Caribbean dengue epidemic, some persons who acquired the infection in the epidemic zone did gain access to this country, though fortunately in the winter season and often in regions where known vectors do not exist.

Second, millions of Americans travel each year to almost all parts of the surface of the earth where they may be exposed to numerous types of arboviruses.

Third, the shifting and unpredictable deployment of hundreds of thousands of military personnel brings them into areas where numerous arthropod-borne agents exist.

Fourth, within our country are many laboratories in which research is being carried out with arboviruses not endemic to the United States and in which the possibility of laboratory infection exists.

Finally, the potential for artificial dissemination of arboviruses in unconventional warfare cannot be ignored.

Between 150 and 200 arboviruses have now been discovered. Although the importance of many as causes of human disease remains unevaluated, others have repeatedly proved themselves to be of major concern – some, like certain of the encephalitides, in fairly well defined geographic regions, and others, like the dengues, circumnavigating the globe in periodic major epidemic spreads.

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Prevention of arbovirus infections has been considered in terms of vector control and immunoprophylaxis. Both are individualized measures and both are highly complex. I will restrict my comments to the general problem of immunoprophylaxis, which comes more directly under the responsibility of the physician, emphasizing some of the problems and reviewing briefly its current status.

Without getting into the intricacies of the pathogenesis of arbovirus infections, which still bears much clarification, it is reasonably clear that recovery from infection is associated with the development of specific immune processes and that subsequent resistance to disease upon reexposure is associated with the persistence of immune mechanisms. The nature of the immune response is incompletely defined and, short of direct challenge, the only laboratory tools for detecting and measuring it are limited to certain procedures for studying serum antibodies, i.e., hemagglutination inhibition, complement fixation and neutralization tests. The correlation between antibodies measured by these techniques and resistance to disease upon challenge is not always good. I should like to stress the need for additional basic research into the pathogenesis and mechanisms of immunity in arbovirus infections. Nevertheless, the existence of acquired immunity does open the way for development of preventive measures on empirical grounds.

Immunoprophylaxis against disease caused by arboviruses, just as with many other infections, has made use of two general procedures:

1. *Passive immunization* by the administration of preformed antibodies in the form of convalescent, immune, or hyperimmune serum.
2. *Active immunization* by the administration of killed or living vaccines.

A combination of these two methods has been used in a *passive-active immunization* procedure, such as in certain early attempts to produce immunity in laboratory workers against yellow fever virus by giving immune serum plus living modified yellow fever virus.

PASSIVE IMMUNIZATION

Passive immunization is no longer used to any significant extent for preexposure protection, but there is considerable current interest in it as a means of preventing disease *following* exposure, such as in laboratory accidents or after tick bite in areas where tick-borne viruses are prevalent. Unfortunately, we are greatly hampered here by lack of precise information, especially as it applies to man.

There is no doubt that, with many arboviruses, the administration of sufficient quantities of specific immune serum prior to inoculation or shortly thereafter will prevent disease in animal model systems. Presumably, this acts by neutralizing the virus at or near the site of infection and prevents viremia and dissemination. The early studies with yellow fever virus in rhesus monkeys showed that fatal infection could be prevented with antiserum. Nevertheless, when this was applied to man in the form of biweekly injections of convalescent serum, disease continued to occur in exposed personnel. Obviously, the quantity of antibody administered must have been a critical factor. Additional observations in man were not made because of the introduction of vaccines.

The Russian experience with the administration of Russian spring-summer encephalitis antiserum to persons experiencing tick bite suggests that the incidence of disease may be lowered significantly.

Studies with other viruses in animals over the years have revealed a wide variety of results depending upon the virus, the host-animal employed, the route and size of virus challenge, and so forth. In some systems, minimal levels of passively transferred antibody seem to offer protection; in others, very large quantities are required.

Quantitative data are not available for man, and results might vary considerably from virus to virus. In addition, two other factors complicate the use of passively transferred antibodies. These are:

1. The risk of allergic reactions, such as anaphylaxis or serum sickness, when animal sera are the source of the antibodies; and
2. The risk of hepatitis following the use of human serum that has not been specially processed to reduce this complication.

I have stressed some problems associated with passive immunity in arbovirus infections because of the current interest in its use after laboratory accidents, and I wish to prevent investigators from placing unwarranted reliance upon it in its present state of development, even though its use must be continued under these conditions in the absence of superior methods.

ACTIVE IMMUNIZATION

Prevention of disease by preexposure *active immunization*, when available, is the most desirable form of immunoprophylaxis. This depends upon stimulation of immune mechanisms in the subject himself and is usually accomplished by injecting viral antigen, either as a killed, noninfectious virus suspension or as a living attenuated strain of virus.

Killed Virus Vaccines

Killed virus vaccines require relatively large amounts of viral antigen, properly deprived of infectivity and in stable form. These conditions immediately pose a series of problems.

Production of Adequate Antigenic Mass. Attainment of an adequate antigenic mass has been a serious problem over the years. Mouse brain, chick embryo, and tissue cultures have all been employed, each with its advantages and disadvantages. At times, procedures which yielded vaccines of reasonable potency on a laboratory scale failed to do so when scaled up for volume production, as occurred with a chick embryo Japanese encephalitis vaccine some years ago.

The problem varies considerably from virus to virus. In tissue culture systems, the rate of thermal inactivation of virus may be large with respect to the rate of virus maturation and release so as to prevent the building up of high antigen titers.

Killing Virus and Stabilizing Antigens. Rendering a vaccine completely noninfectious without destroying its antigenicity has been troublesome in some instances. With one Venezuelan equine encephalomyelitis vaccine, evidence was obtained that virus infectious for man was still present even though laboratory tests for residual infectious virus were negative. When the vaccine was rendered completely noninfectious for man, it also lost its capacity to stimulate antibody formation. Formalin has been used most frequently for rendering virus non-infectious, but other substances, such as betapropriolactone, have also been studied.

HOST MATERIALS CONTAINED IN VACCINE. Mouse brain and chick embryo vaccines contain a large amount of host material that is objectionable because of possible allergic reactions. Concern has been expressed repeatedly about the possibility of allergic encephalitis following the use of mouse brain vaccines, although documented instances of such a reaction are rare, if not nonexistent. Nevertheless, attempts have been made to circumvent this problem either by the use of suckling mice in which the antigen(s) responsible for the allergic encephalitis are minimal or absent or by selective removal of brain material.

EXTRANEOUS AGENTS. Mice, chick embryos, and tissue cultures frequently carry extraneous passenger viruses whose potential hazard to human beings is still unevaluated. These agents constitute potential problems, not only for the living vaccines, but also for killed virus vaccines in which the passenger agent might theoretically not be inactivated by the same treatment that is effective for the vaccine virus. This represents one of the areas of greatest uncertainty in vaccine development today and constitutes one of the greatest deterrents to bringing an experimental vaccine up to the point of practical use. It is, of course, not peculiar to arbovirus vaccines.

MULTIPLE DOSES ARE REQUIRED. The requirement for multiple doses of killed vaccine over a period of time before the development of a significant antibody response is disadvantageous on several counts: multiple doses increase the hazard of allergic reactions to host components; during a sharp epidemic, antibody response may be too slow to be effective during the period of risk; and multiple doses constitute a serious logistic problem when large numbers of people must be immunized.

Regardless of these disadvantages, killed vaccines are still considered to be useful and may be the only practical means for immunoprophylaxis in many instances. Certainly, the period between initiation of developmental work and the production of a usable product is likely to be significantly shorter with killed vaccine than with living attenuated vaccine.

At the present time, no killed arbovirus vaccines are licensed for use in man in this country, although veterinary vaccines have been in use for some years.

Living Attenuated Vaccines

Living attenuated vaccines, which act by producing a subclinical or modified infection, offer certain advantages over killed vaccines: only a single dose is required; immunity develops rapidly – in 7 to 10 days with yellow fever vaccine – obviously a great advantage in an outbreak or epidemic; the immunity may be more effective; and immunity may last for a relatively long period of time.

In spite of these advantages, several problems prevent ready development of attenuated living arbovirus vaccines:

DEVELOPMENT AND SELECTION OF A STRAIN OF PROPER ATTENUATION. No good markers exist that are reliable laboratory indicators of proper attenuation for man. A strain may not be attenuated enough and result in considerable reaction or serious disease. This makes most difficult the decision of when to test in man a potential candidate attenuated strain derived from a virus that naturally causes serious disease. It may be too attenuated and fail to produce an immunizing infection, as occurred in a recent attempt to produce an attenuated living Japanese encephalitis virus vaccine. Laboratory manipulation may give it new, undesirable properties—such as increased neurovirulence in dengue virus strains. The problem is illustrated by findings with attenuated dengue virus strains. Four candidate strains were developed. All produced fatal encephalitis in suckling mice. None produced encephalitis in rhesus monkeys but all produced febrile responses of varying degrees. The strain that produced the greatest febrile response in monkeys proved to be the most attenuated for man and is a strain under current testing as a vaccine.

MAINTENANCE OF DESIRED CHARACTERISTICS FROM LOT TO LOT. This requires careful seed pool regulation and characterization.

PASSENGER VIRUSES IN THE HOST TISSUE. Passenger viruses in the host tissue pose very great and unevaluated problems, especially since it is not possible to inactivate them. Tissue cultures and chick embryos free of known passenger agents have been obtained, sometimes with great difficulty and at high cost. Passenger viruses in mouse tissues are currently posing a difficult problem. It is unknown whether these agents pose any significant hazard to man, but there is great reticence at this time to expose man unnecessarily to viral agents that produce leukemia in mice or tumors in hamsters.

STORAGE STABILITY OF VIABILITY. It is important to be able to administer the desired number of infectious units per dose of vaccine without elaborate continuous laboratory monitoring. This problem has been minimized with the 17D yellow fever vaccine by careful regulation of the shipping and storage conditions and by the distribution of vaccine to certain designated vaccination centers where presumably specially trained personnel handle and administer it.

POSSIBLE ACQUISITION OF VIRUS BY ARTHROPODS FROM VACCINATED PERSONS AND REVERSION TO VIRULENCE. Fortunately, the dengue viruses quickly lose their capacity to multiply in mosquitoes after a relatively brief period of laboratory manipulation. This may not, however, be a general phenomenon.

Another problem common to both classes of vaccine is that of obtaining proof of efficacy in man. With the exception of a few instances, like dengue fever, in which challenge is without undue risk, proof of efficacy can be derived only from field trials carried out during natural occurrence of the disease. This poses many difficulties.

Table 1 summarizes the current status of vaccines, both killed and living attenuated, for protection against infection by a number of arbovirus agents. Most are beset with one or more of the problems just outlined. Note that progress has been poor with vaccines for protection against the most important arbovirus diseases in the United States—namely, eastern, western, and St. Louis encephalitis, diseases that produce epidemics of varying severity at relatively frequent intervals. Greatest progress has been made in the United States with arbovirus diseases of potential military importance that are endemic in other parts of the world, and by scientists in other countries, like Japan and Russia, where certain arbovirus infections are considered to be of major public health importance. In this country, vaccines showing some current progress are killed products for protection against Japanese encephalitis and Rift Valley fever and living attenuated vaccines against Venezuelan equine encephalomyelitis and type 1 dengue

Table 1. *Status Summary of Some Arthropod-Borne Virus Vaccines*

VIRUS*	KILLED VACCINES					ATTENUATED LIVING VACCINES				
	Tissue† Source	Status				Tissue† Source	Status			
		Lab. Exper.	Human				Lab. Exper.	Human		
			Exper.	Field	Lic.§			Exper.	Field	Lic.§
Group A										
EEE	MB		(lab.)‡							
	CE		(lab.)		(vet.)					
	TC	+								
WEE	MB		(lab.)							
	CE		(lab.)		(vet.)	TC	+			
	TC	+								
VEE	CE		(lab.)			TC		(lab.)		
	TC	+								
Group B										
YF						MB			+	(not U.S.)
						CE			+	+
JE	MB			+						
	CE			+		TC	+			
	TC	+	+							
Dengue-1						MB			+	
Dengue-2						MB		+		
Tick-borne	MB		(lab.)	+	(not U.S.)	TC		+		
	CE	+								
	TC			+	(not U.S.)					
WN						TC	+			
SLE	MB	+								
Other										
Colorado tick	TC	+								
Rift Valley	TC		+							
Sandfly						MB		+		

*Viral agents: EEE, eastern equine encephalomyelitis; WEE, western equine encephalomyelitis; VEE, Venezuelan encephalitis; YF, yellow fever; JE, Japanese encephalitis; WN, West Nile; SLE, St. Louis encephalitis.

†Tissue source: MB, mouse brain; CE, chick embryo; TC, tissue culture.

‡(lab.), has had use in laboratory personnel at risk.

§Lic., licensed for commercial manufacture and use in U.S.; (vet.), licensed veterinary product.

fever. An attenuated strain of western equine encephalitis virus has been developed and has been tested in domestic animals as a veterinary product but no trials have been made in man.

Japanese scientists have developed a partially purified killed mouse brain vaccine against Japanese encephalitis that is widely used in Japan. Russian scientists have developed and used in large-scale field trials both mouse brain and tissue culture killed vaccines against Russian spring-summer encephalitis virus.

CROSS IMMUNITY

The problem of arbovirus vaccines cannot be discussed without consideration of the matter of cross immunity. With such a large number of arboviruses and with the tremendous effort required to develop even a single vaccine suitable for human use, attention has been directed toward serologic cross reactions as a possible clue to significant cross immunity. Among arboviruses of Group B for example, which contains many important causes of human disease, relatively strong serologic cross reactions occur, and among certain closely related viruses, like the dengue viruses, some degree of transient cross immunity following infection has been demonstrated in man. It would be highly desirable to be able to produce a broad immunity by a simplified regimen consisting of a few selected vaccines. Some exploratory efforts have been made along these lines, without uniform results. Using suppression of viremia in monkeys as a guide, Price and his co-workers have observed some degree of broadened immunity with sequential immunization with certain Group B agents. On the other hand, a few years ago we were able to induce type 1 dengue neutralizing antibodies in man by giving 17D yellow fever virus to persons who had had Japanese encephalitis virus infection. In spite of the antibodies, these persons were not immune to dengue upon challenge.

Another theoretically disturbing, but unproved, hypothesis, derived from speculations about the pathogenesis of the dengue shock syndrome or so-called hemorrhagic dengue, involves the possible cross-allergic sensitization that might develop when vaccines of several serologically related viruses are given in close sequence.

At the opposite pole from broad cross immunity are the disturbing observations that strains of a given virus from different geographic regions may differ significantly among themselves in antigenic makeup and that laboratory manipulation may select antigenically distinct virus populations. It is obvious that these opposing sets of observations require considerably more investigation before problems of immunity are solved.

Finally, attention should be called to a mechanism that has been established to provide experimental vaccines to those at unusual risk, like laboratory workers, despite the increasingly stringent Food and Drug Administration regulations on experimental products. Because of these regulations, the former practice of distributing experimental vaccines to one's colleagues upon request is under a legal dark cloud which, in my opinion, has been extended far beyond reasonable limits of usefulness. To continue to provide laboratory workers with some sort of protection within the framework of the new federal regulations, a special service has been established at the Communicable Disease Center, called the Investigational Vaccines Program, through which such experimental products can be distributed to qualified persons. However, no arbovirus vaccine has yet been entered into this program.

I began this paper with an apology for the status of arbovirus vaccines and I must close it in much the same vein. We have not yet accomplished that which is most certainly possible.

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Enterovirus Infections of the Central Nervous System

The Present and Future of Poliomyelitis

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It is now 12 years since the introduction of successful immunization against poliomyelitis with inactivated vaccine, and more than five years since live attenuated oral poliovirus vaccines were licensed in the United States. A review of what has been accomplished as a result of extensive use of these two products over a short span of years constitutes one of the great success stories in modern medicine. Yet this is not the time for complacency, nor is it likely that there will be such a time, for we are continually reminded by the occurrence of poliomyelitis epidemics in various countries that constant vigilance must be practiced if we are to continue our current success in the prevention of this disease.

In the following short discussion of so large and complicated field, I will concentrate on a few major areas: (1) poliomyelitis incidence in several representative countries in which different types of vaccination programs have been carried out; (2) what has been learned in the past decade about the clinical epidemiology and immune mechanisms in poliomyelitis, particularly as a result of the unique opportunity afforded by live virus vaccines to carry out *experimental epidemiology* in man; (3) what problems and complications have been associated with the two types of vaccine; and finally, (4) what the future might hold in relation to paralytic disease caused by polio- and other enteroviruses.

POLIOMYELITIS INCIDENCE IN RELATION TO IMMUNIZATION PROGRAMS

The history of epidemic poliomyelitis in the United States began around the turn of the century with the appearance of several sizeable epidemics on the eastern seaboard, followed by an extremely severe outbreak in New York City and New England in 1916. As is characteristic of this disease, once epidemics made their appearance, they continued to

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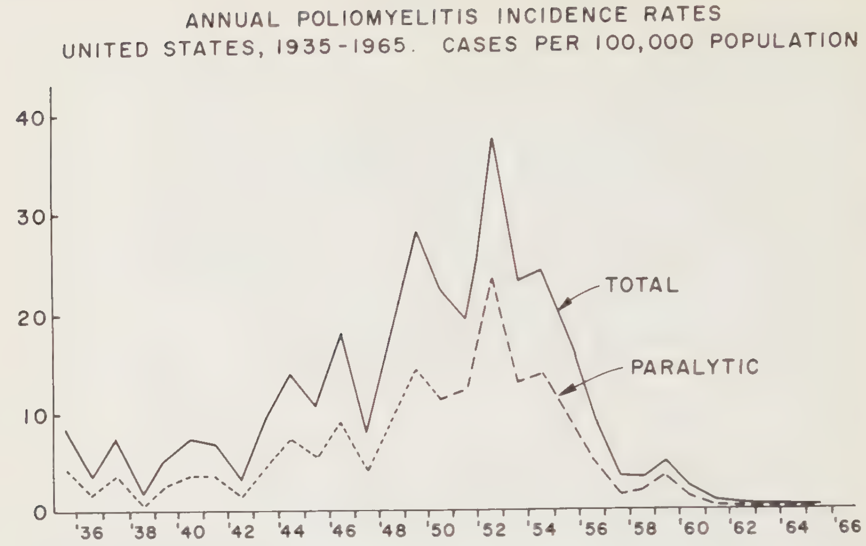

Figure 1. Poliomyelitis incidence rates; data from Communicable Disease Center Surveillance Reports No. 283 (1964), 287 (1965), and 288 (1965). Paralytic cases before 1951 assumed to be 50 per cent of the total. Since 1951, cases reported as unspecified were prorated among paralytic and nonparalytic.

recur, and in the late 1940's and early 1950's the problem reached alarming proportions. Figure 1 illustrates the course of events in the United States between 1935 and 1965. The marked impact of inactivated (killed) Salk-type vaccine on the incidence of the disease is illustrated by the fall in paralytic case rates from 13.9 in 1954 to 0.5 in 1961. Live attenuated Sabin oral poliovirus vaccines were licensed in the United States in 1961–1962, and since this time there has been a further striking reduction in cases to the lowest figure since reporting began (Fig. 2), viz., a nationwide total of 61 paralytic cases in 1965!

The experience of the United States is far from unique. In other parts of the world, where vaccination against poliomyelitis has been efficient, similar patterns of sharp decline in incidence have followed.[23, 27] The picture in several representative countries is shown in Figure 3. The data for Denmark[30] and Sweden[3] are of particular interest because they indicate what can be accomplished by killed virus vaccine alone (locally manufactured) in such highly developed, economically advanced countries. In both of these Scandinavian countries, immunization of a high proportion of the child and young adult age groups resulted in a sharp reduction of cases in the late 1950's; this was followed by an increased incidence in 1961 when small outbreaks occurred in both countries, and subsequently virtually no cases in the period 1962–1965. In 1963 and early 1966, the Danish population has received oral vaccine, but in Sweden only inactivated vaccine has been used routinely.

In Czechoslovakia, on the other hand, where epidemic poliomyelitis is a relatively new disease, there was less success in preventing epidemics with inactivated vaccine, which was introduced in 1957; oral vaccination was therefore started in 1959, and a nationwide program was

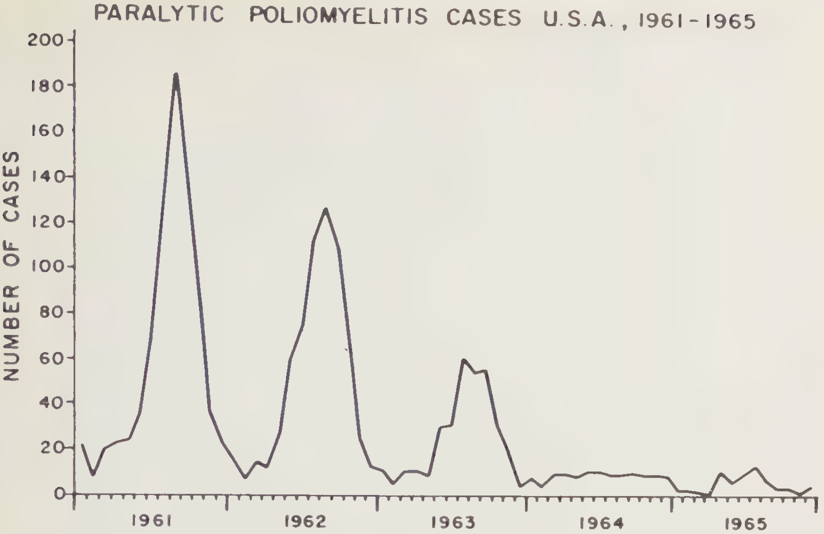

Figure 2. Decline of paralytic poliomyelitis after introduction of oral vaccine. (Data from C.D.C. Poliomyelitis Surveillance Report No. 288, 1966.)

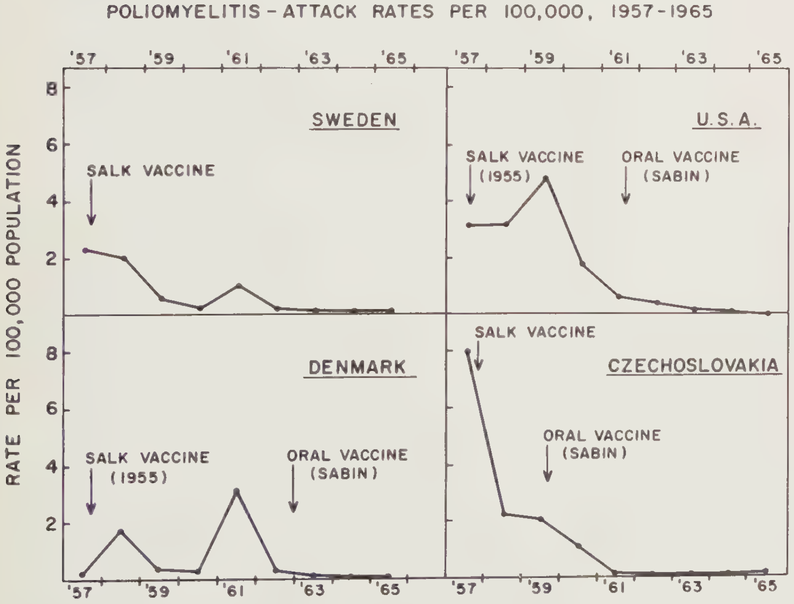

Figure 3. Impact of vaccination on poliomyelitis incidence in Sweden,[3] Denmark,[30] Czechoslovakia,[23, 33] and U.S.A. (C.D.C. Surveillance Report No. 283, 1964).

begun in 1960. By 1961, the incidence of the disease was reduced to zero and has remained so since.[23, 33] Similar striking and rapid reductions in incidence have occurred in many other countries in which oral vaccine has been diligently used on a nationwide scale.[23]

MECHANISMS OF VACCINE-INDUCED IMMUNITY; RELATION TO EPIDEMIOLOGIC FACTORS

These impressive results, using different approaches to immunization, illustrate the importance of local epidemiologic factors in the control of poliomyelitis. Such factors relate directly to the nature of the immunity resulting from killed virus vaccine and from live virus vaccine; this has been shown to be different, quantitatively and qualitatively. The effectiveness of inactivated vaccine is mediated primarily through the presence of circulating antibody which presumably blocks virus in blood and tissues. In addition, however, an important aspect is the presence in the pharynx of local antibody which is apparently capable of neutralizing poliovirus at the site of entry, thus acting as a first line of defense.[13, 30] The relationship to serum antibody is a quantitative one, and significant suppressive potential is present in throat secretions only if the serum antibody titers are relatively high.[2, 17] Correspondingly much higher serum titers are required to suppress virus multiplication in the intestinal tract – levels which are not ordinarily attained with killed virus vaccine.

The effectiveness of the pharyngeal barrier to infection which inactivated vaccine induces is enhanced by epidemiologic circumstances in which spread of polioviruses is attributed primarily to the pharyngeal-oropharyngeal route. Such circumstances prevail in populations with high economic development and superior sanitary environments such as exist in the small Scandinavian countries. When potent inactivated virus preparations are available and antibody titers are maintained at high levels by repeated injections of vaccine, the circulation of wild polioviruses in such populations has been strikingly reduced, and, as Figure 3 shows, paralytic cases have declined to virtually zero.[3, 6] There is, however, the ever present possibility of the introduction of wild virulent strains into such populations, as apparently occurred in Sweden and Denmark in 1961 (Fig. 3). Under these circumstances, inactivated vaccine alone has proved inadequate, and epidemics involving vaccinated as well as unvaccinated persons have occurred in well vaccinated communities.[1, 4]

In different types of epidemiologic situations, i.e., among populations living under conditions of poorer sanitation and hygiene, and where poliomyelitis is chronically endemic, there is evidence that the fecal-oropharyngeal route of spread of polioviruses is the more important one. Under these circumstances, which prevail in many parts of the world, inactivated vaccine is far less effective than is oral vaccine in reducing circulation of wild polioviruses. The explanation lies in the ability of oral vaccine to induce not only serologic immunity, but also a high degree of resistance to reinfection of the alimentary tract – the pharynx and the gut.[11, 15] The immunity resulting from live virus vaccine thus parallels that achieved by inapparent infection with naturally occurring polioviruses, and a well vaccinated community presents a far more solid barrier to invasion by wild virulent strains than is the case following immunization with killed virus vaccine.

Because of this superior immunogenicity, the live attenuated virus vaccine has been adopted in most parts of the world as the immunizing agent of choice in the control of poliomyelitis. Additional advantages include reduced cost and ease of administration; the speed with which the immune response develops (7 to 10 days) which makes the vaccine effective in controlling epidemics; and persistence of immunity similar to that which follows natural infection with wild polioviruses. In the United States, The American Academy of Pediatrics recommends oral poliovirus vaccination for all children beginning at two to three months of age.

SAFETY OF ORAL VACCINES

Early field tests of increasing size and later large-scale vaccination programs involving hundreds of millions of persons have established the safety of oral vaccines containing the Sabin strains. However, careful surveillance has indicated that a probable minimal risk has attended the use of Type III, and possibly Type I. On the basis of extensive sifting of clinical, laboratory, and epidemiologic evidence, a U.S.P.H.S. Surgeon General's Advisory Committee on Oral Poliomyelitis Vaccine estimated in 1964 that the risk was approximately 1:6 million doses for Type I, negligible for Type II, and 1:2.5 million doses for Type III. The difficulties in establishing a definite association in any given case proved virtually unsurmountable, and ultimate decisions as to "compatibility" with vaccine-association were based largely on epidemiologic evidence.[7, 9, 27] Part of the problem stems from the inability to classify an isolate definitely as a vaccine-related strain, even if all available laboratory methods are used. After passage in the human intestinal tract, in-vitro markers such as "rc T/40°" and the "d" marker frequently show shifts from negative to intermediate or positive, particularly if the strain has been recovered some weeks after vaccine ingestion.[19] Furthermore, there is no clear relationship between these marker shifts and increased neurovirulence for the monkey. It was hoped that the intratypic serodifferentiation tests (ISD) of Wecker[31] and of McBride,[18] which have nothing to do with virulence but measure antigenic stability, would provide the necessary guide for recognition of vaccine-derived strains in the field. Extensive investigations by Nakano et al.[20] indicate that the Type I strains recovered within one week of vaccination are highly stable and the reaction is "vaccine-like" in both ISD tests. After this time, however, there is a tendency to "antigenic drift," and the strains may demonstrate the antigenic characteristics of wild strains. The Type III Sabin vaccine strain, on the other hand, is remarkably stable and shows virtually no antigenic change even if excreted many weeks after vaccine ingestion. However, seven wild Type III strains, recovered before the introduction of oral vaccine, were found to have the antigenic marker of the attenuated Sabin Type III.[20] In some circumstances, then, a strain of Type I or Type III may be characterized as vaccine derived with a degree of confidence, but in other situations this may not be possible.

The 1964 report to the Surgeon General[21] called attention to the apparently greater risk of oral vaccine to adults than to children. However, since the report was made, a modified derivative of the original Leon 12 a,b strain (Sabin Type III) has been used in some of the currently available vaccines. The modification was achieved by extraction of the infectious RNA which has been inoculated into tissue culture cells with resultant production of complete virus. The Sabin Type III strain so obtained has been reported by Stones et al.[25] to have less neurovirulence for the monkey's central nervous system than does the Type III United States Reference Vaccine Na-2. We have tested two lots of the modified Type III vaccine virus in infants and young children. Virus excretion and antibody conversions occurred in all of the 19 vaccinees aged five months to four years who were tested. In-vitro genetic markers of 99 of the strains excreted over a period of six weeks after virus ingestion indicated complete stability on human passage as measured by the intratypic serodifferentiation test (modified McBride). Neurovirulence tests by Stones[26] on 88 of the same specimens inoculated into monkeys by the intrathalamic route revealed that, as with the unmodified Sabin Type III vaccine, many of the children excreted virus of increased neurovirulence at some time during the six-week observation period, but the appearance of such strains was erratic and intermittent in fecal specimens from the same child.

Other laboratory-attenuated Type III strains have been investigated by Vonka et al.[28, 29] as potential vaccine candidates. At least one, the USOL-D bac strain, appears to have somewhat less neurovirulence for the monkey than does the Sabin Leon 12 a,b strain; tests in humans have demonstrated its capacity to multiply well in the intestinal tract and to induce satisfactory antibody responses. It would seem likely that the use of either the modified Sabin Type III, or other equally immunogenic strains with similar minimal neurovirulence for the monkey, might provide additional protection against the possibility of vaccine-associated disease. In any event, viewed against the background of the several hundred million doses used, the record of safety of the oral vaccines has been a remarkable one, and compares favorably with any biologic product currently in use.

SIGNIFICANCE OF SPREAD OF ORAL VACCINE STRAINS

One of the questions which troubled investigators in the early days of oral vaccine trials was the capacity of the live attenuated viruses to spread to contacts of vaccinees. Although such strains are not transmitted as readily as are wild virulent ones, infection of exposed susceptibles was documented in institutional populations[11] and in other field trials.[7, 21, 22] The results indicated that close contacts—especially susceptible young children—acquired infection a few days after the vaccinee had ingested virus,[21] and children under two years of age were demonstrated to be the most effective spreaders of the agent.[5] Such dissemination of virus by vaccinees was considered by some to be a potential advantage, but there was concern that after serial human passage the virus might be capable of inducing paralytic disease. This danger has not materialized, however, and extensive use in the field with more than 100,000,000 doses administered in the United States alone has been accompanied by only a handful of possibly vaccine-associated cases in contacts. The reason for this appears to be that, although some change may occur on passage, in the case of the attenuated strains this is not a progressive phenomenon in the direction of neurovirulence.

Evidence bearing on the lack of significant enhanced virulence of vaccine strains on human passage is provided also by long-term investi-

Table 1. *Recovery of Polioviruses from Sewage** (Middletown, Connecticut, 1965).

	SAMPLES		NO. POLIOVIRUSES ISOLATED			OTHER VIRUSES		
			Type					
	No. Tested	No. Pos.	I	II	III	Cox. B2	Cox. B4	U†
Jan.–March	13	13	10	8	9			
April–June	13	13	9	11	8			
July–Sept.	11	10	8	4	4			
Oct.–Dec.	12	12	9	6	9	2	1	2

*Line serves 20,000 population.
†Untyped.

Table 2. *Recovery of Polioviruses from Unvaccinated Children Aged Two Months to Five Years* (Middletown, Connecticut, 1965).

	RECTAL SWABS		NO. POLIOVIRUSES ISOLATED		
			Type		
	No. Tested	No. Pos.	I	II	III
Jan.–March	44	2	2	0	0
April–June	65	5	1	2	1
July–Sept.	39	7	4	4	1
Oct.–Dec.	31	1	0	1	0
TOTAL	179	15 (8%)	7	7	7

gations in our laboratory. Continuing observations over a five-year period following a community-wide oral vaccination program in Middletown, Connecticut, a city of some 30,000 inhabitants, has indicated that vaccine-like polioviruses are regularly present in the sewage, yet there has been no evidence of associated disease. Table 1 gives the isolation results for one year (1965). Samples taken at weekly intervals for five years have yielded similar findings: at least one type of poliovirus (and frequently all three) has been present in almost every specimen tested since the introduction of oral vaccine and its use as the standard immunizing agent for susceptibles by the Health Department and local clinicians. Results of in-vitro marker tests on the strains isolated have been similar to those obtained with strains recovered from vaccinees.[19, 20] That there is a certain amount of circulation of vaccine strains and that spread from vaccinees to susceptibles occurs, has been documented by examination of pre-oral-vaccine rectal swabs from children attending the Well Child Conference. Some 15 of 180 or approximately 8 per cent of children tested in 1965 were already excreting one or more types of poliovirus before being immunized (Table 2). As with the strains isolated from sewage, in-vitro marker patterns indicated characteristics similar to the vaccine strains.

POLIOMYELITIS—CURRENT PROBLEMS IN PREVENTION

Despite the availability of effective means of preventing paralytic poliomyelitis and virtually eliminating it from wide geographical areas, outbreaks of the disease have continued to occur in various parts of the world in the past few years. In 1965 the United States had a record low year with only 61 paralytic cases reported (see Fig. 2). In 1966, the situation was different, however, for by the end of August, 46 cases with two deaths had already occurred in a Type I outbreak in southern Texas. Characteristically, the cases were virtually all in young preschool children who had never been vaccinated.

The experience illustrates several points: first, that wild virulent polioviruses are still lurking about and finding suitable soil in which to perpetuate themselves; second, young children still constitute the bulk of susceptibles and are the chief disseminators of the virus. As long as a sizeable number of this age group remains unprotected in any community, it would seem inevitable that paralytic poliomyelitis will return, sooner or later. The implications are clear: if we hope to eliminate outbreaks of the paralytic disease it is necessary to make vigorous efforts to find (which is no easy matter) and to immunize all preschool children. For optimum protection of individuals and of the population at large, community-wide oral vaccination campaigns are recommended as a first step, again with strong emphasis on the preschool age group. But such programs are not enough: they must be followed by continued vaccination of the new susceptibles born into the community or entering from other areas. This may be accomplished by routine immunization beginning at two or three months of age, as is done in the United States, or by yearly community programs for all infants two months and older born since the previous program, which seems to be an easier method for some countries. Unless some mechanism is provided for maintaining a high level of immunization of young children, the situation becomes a dangerous one, for the circulation of wild polioviruses, although not eliminated, is presently greatly reduced in the United States and in other countries where immunization has been practiced extensively. New susceptibles appearing in the community are therefore not exposed to beneficial immunizing infections with naturally occurring attenuated polioviruses, and a build-up of young susceptibles therefore follows. When a virulent strain is introduced into a setting of this type, an epidemic such as the one which occurred in Texas in 1966 ensues.

This pattern of epidemics emerging after extensive vaccination campaigns has been observed in other countries, too. In 1964, for instance, a sharp outbreak occurred in Jamaica.[16] It was confined almost exclusively to those born in the two years since the mass immunization campaign of 1962 which was *not* followed with an on-going program to take care of new susceptibles. Similar epidemics have occurred elsewhere, particularly in tropical and semitropical countries where there is extensive circulation of enteroviruses among the child population.

There are, of course, still many countries in which it has not yet been possible to carry out adequate vaccination against poliomyelitis. Many of these have had primitive sanitary conditions and poliomyelitis has been no threat to them in the past, but with the improvement in global sanitation and changes in the way of life, the past is no measure of the future. Epidemics occur and will continue to appear. The one in Honduras in 1965 is a good example.[10] Some 222 cases were reported, 90 per cent in children under five years; there were nine deaths. It is probable that we shall see similar epidemics, particularly in developing countries where economic and other problems have delayed institution of adequate control measures.

While it is far better to prevent epidemics rather than to try to stop them once they have begun, oral vaccine can be used effectively to cut short an epidemic. This requires the prompt identification of the virus type causing the outbreak, and rapid administration of the corresponding *monovalent vaccine type* to the young child population. Unfortunately there has been a tendency to use trivalent vaccine in several recent epidemics due to Type I virus.[10] This is not an optimum procedure because of the low rate (20 to 30 per cent) of Type I vaccination takes induced with the first dose of trivalent vaccine in young triple-negative children. While interference due to intestinal multiplication of a heterotypic poliovirus has some effect in preventing infection with the epidemic strain, this is not as effective in limiting the spread of an epidemic as is specific immunity to the prevalent type.

THE FUTURE – POLIOMYELITIS AND OTHER ENTEROVIRUS DISEASES OF THE CENTRAL NERVOUS SYSTEM

As the foregoing discussion has stressed, it is possible to eliminate paralytic poliomyelitis from large areas, and to reduce sharply the circulation of wild virulent polioviruses. The question has been repeatedly raised, Will other enteroviruses become more neurovirulent and take over, so to speak, the role of the departing polioviruses as causes of severe CNS disease? After five years' experience, the answer seems to be a clear cut NO. The three poliovirus types represent but a small fraction of the world of enteroviruses, which grows steadily, the family now numbering over 60 distinct serotypes. The presence or absence of polioviruses has little impact on the behavior of other members of this group, which, although they share similar biochemical-physical properties and epidemiologic characteristics, present certain differences in terms of biologic behavior. These differences are not absolute, however, and the spectrum of disease-producing potential of all enteroviruses, polio-, Coxsackie, and echo-, is similar in that it ranges from completely inapparent infections to fatal CNS involvement. With all of the viruses, including polioviruses, inapparent infections are far commoner than apparent ones. The number and variety of clinical syndromes which these agents can induce is large and growing larger, but as far as the central nervous system is concerned, aseptic meningitis is the main expression of neurotropic potential of nonpolio-enteroviruses. A large number of Coxsackie and echoviruses have been associated with this syndrome and some have caused extensive epidemics.[14] The incidence of reported cases of aseptic meningitis in the United States has not changed greatly in recent years, at a time when poliomyelitis incidence has been declining steadily (Fig. 4). At the same time, there has been no increase in incidence of paralytic disease due to Coxsackie and echoviruses. These viruses, then, seem to go their independent ways.

The Coxsackie and echoviruses most commonly associated with aseptic meningitis are the Coxsackie B group, Coxsackie A 9, 7, and certain echoviruses, particularly 4, 6, 9, and 11. Since these agents induce CNS infections, it is not surprising to find that they are the main ones which have been implicated in the rare cases of severe encephalomyelitis due to enteroviruses other than polioviruses. Since the early 1950's when Steigman first called attention to the association of Cox-

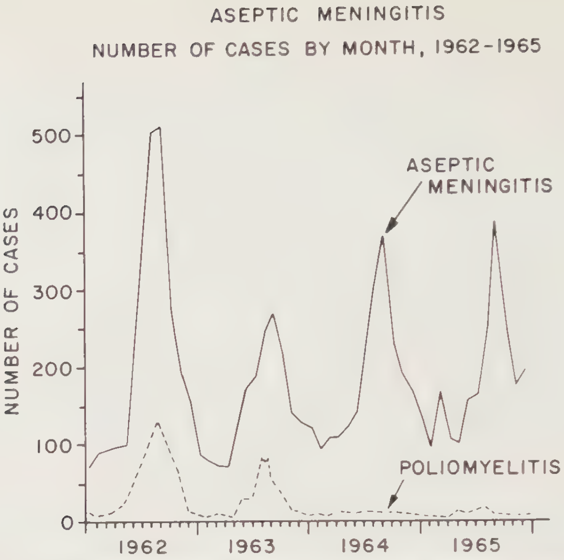

Figure 4. Reported cases of aseptic meningitis remain at essentially the same annual level while poliomyelitis has declined sharply. (Data from C.D.C. Surveillance Report No. 288, 1966.)

sackie B viruses with paralytic disease in man, a number of such cases due to these and other enteroviruses has been reported.[12, 14] During epidemics of echoviruses 6 and 9 a significant incidence of mild muscle weakness has been noted, but this has been a transient phenomenon and persistent paralysis has been rare with these and the other nonpolio-enteroviruses associated with CNS disease. Fatal cases with isolation of virus from spinal fluid or CNS are few – not more than 12 or 15 have been reported. This excludes the Coxsackie B encephalitis and myocarditis of the newborn, which is a generalized disease and highly fatal.

In the overall picture, then, it seems clear that the clinical picture of paralytic poliomyelitis is caused primarily by polioviruses, and has very rarely been associated with other enteroviruses. There has been no evidence so far of increased CNS pathogenicity of Coxsackie and echoviruses following the decline in poliovirus infections, and there seems no reason to suspect that this will happen in the future. It is never safe to discount the unpredictability of biologic behavior, however, and this should be remembered in connection with the future of the enterovirus family.

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Rabies: Incidence and Immunization in the United States

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In spite of the fact that we usually have fewer than five human rabies deaths each year, this virus disease continues to be a health problem in this country. Rabies occurs in our animal populations; humans are exposed to rabies by the bite of rabid animals, and about 25,000 patients each year receive specific prophylaxis as the result of that exposure.

INCIDENCE AND DISTRIBUTION OF RABIES IN UNITED STATES

With the now long-established routine successful vaccination of dogs against rabies in many areas of the United States, there has been a gradual but definite shift in the species of animal serving as the important reservoirs of the disease. Prior to World War II the major reservoir was dogs, and dog bites were the chief source of rabies exposure of man. However, with increasing use of readily available, potent rabies vaccines (both live virus chick embryo type and phenolized brain tissue type) for pre-exposure immunization of dogs, the incidence of rabies in canines has steadily dropped.

Rabies has long been present in our wildlife and all mammalian species are naturally susceptible to the infection (see Table 1). However, the relative susceptibility of certain species seems to be the factor which determines the important wildlife reservoirs of rabies. Foxes and skunks are highly susceptible and represent the greatest problem in the ecology of rabies in this country. Although these two species coexist in many parts of the country and rabies may occur in both animals in a single area, there has been a tendency for a concentration of the problem in foxes in the eastern part of the country along the Appalachian range and in skunks in the Midwest and along the Pacific coast. Because of the declining incidence of rabies in dogs, the relative importance of the wild species has increased. An actual increase in the number of cases in these wild species may be due to increased surveillance because of increasing opportunity for contact of the human population with these animals and increasing population densities of the species involved.

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Table 1. *Incidence of Rabies in the United States by Type of Animal—1953-1964**

YEAR	DOGS	CATS	FARM ANIMALS	FOXES	SKUNKS	BATS	OTHER ANIMALS	MAN	TOTAL
1953	5,688	538	1,118	1,033	319	8	119	14	8,837
1954	4,083	462	1,032	1,028	547	4	118	8	7,282
1955	2,657	343	924	1,223	580	14	98	5	5,844
1956	2,592	371	794	1,281	631	41	126	10	5,846
1957	1,758	382	714	1,021	775	31	115	6	4,802
1958	1,643	353	737	845	1,005	68	157	6	4,814
1959	1,119	292	751	920	789	80	126	6	4,083
1960	697	277	645	915	725	88	108	2	3,457
1961	594	217	482	614	1,254	186	120	3	3,470
1962	565	232	614	594	1,449	157	114	2	3,727
1963	573	217	531	622	1,462	303	224	1	3,933
1964	409	220	594	1,061	1,909	352	238	1	4,784

*Data prior to 1960 from USDA, ARS. Subsequent data from PHS, CDC. Reprinted from CDC Veterinary Public Health Notes.

Other species are involved in the rabies problem. Cats have never been as frequently infected as dogs, yet occasionally there will be reported small isolated groups of cases in cats. Domestic farm animals are still lost due to rabies and the high incidence in wild species in certain areas represents a continuing threat to cattle, horses and pigs. There have been occasional instances of outbreaks of rabies localized in a county area and limited to raccoons. Small rodents do not appear to be an important reservoir.

The geographical distribution of rabies in the United States is shown in Figure 1.

A special situation has existed since 1953 when rabies was found

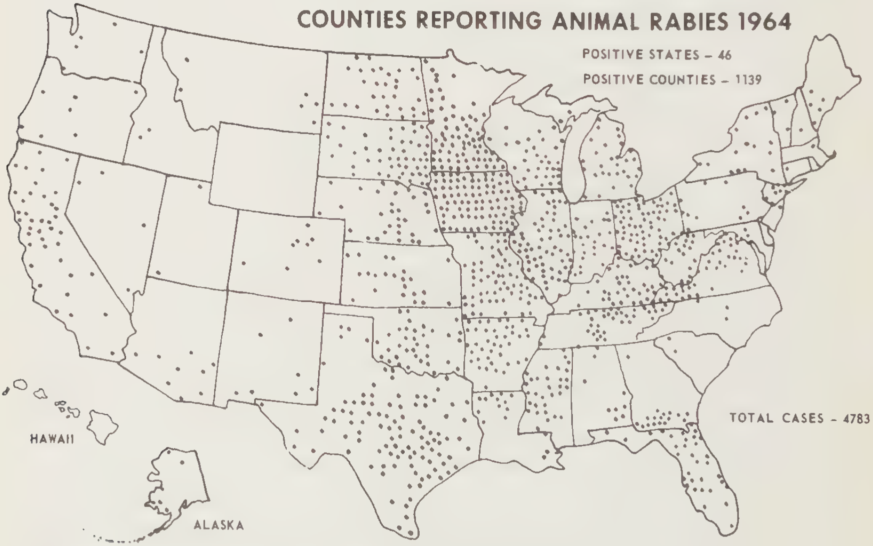

Figure 1. Geographical distribution of rabies in the United States in 1964. (Reprinted from Communicable Disease Center Veterinary Public Health Notes.)

for the first time in the bat populations of this country. It has been known for some years that insectivorous and fructivorous as well as vampire bats were infected with rabies in the Caribbean and Latin American areas. Since 1953, rabies infection has been found in a wide variety of bats in 40 states of the U.S. Bats infected with rabies and capable of transmitting the disease by bite are usually sick at the time and exhibit abnormal behavior as part of the symptomatology of their infection. However, it is known that infectious bats may be in apparent good health for prolonged periods of time before eventually succumbing to their own infection. Therefore, all bites by bats must be considered a potential exposure to rabies. We have had five human deaths in the U.S. due to rabies transmitted by bat bites. There is one other aspect of rabies in bats that must be kept in mind in relation to possible infection of man. In caves infested with large numbers of rabies-infected bats, the disease has been transmitted experimentally through the respiratory tract by aerosol.[4]

TREATMENT OF THE BITE WOUND

The best time to prevent rabies is at the time of the bite. If virus introduced into the bite wound is physically removed or inactivated before it enters cells, prevention can be complete. Many studies have been made to indicate that immediate, thorough cleansing of the wound with soap and water can be very effective.[10] The application of certain chemical agents to inactivate the virus is also indicated (see Table 2). The local application of rabies antiserum on swabs applied to the wound has proved quite efficient in experimental infection.[6] Rabies bite wounds should not be sutured unless absolutely necessary, and then the wound should not be closed tightly.

POSTEXPOSURE SPECIFIC PROPHYLAXIS OF RABIES

The principles involved in the prevention of rabies by vaccine are the same as in Pasteur's day, but more modern techniques have improved the quality and potency of the vaccines used. From the immunological standpoint, the situation in rabies prophylaxis is very abnormal since the attempt is made to actively immunize the patient *after* the causative virus has already been introduced into the body. This is possible only because of the long incubation period in this disease and is also the reason why time factors are so important in the medical handling of a patient bitten by a rabid animal.

A new and different approach to rabies prophylaxis in severely exposed individuals was indicated since the usual course of vaccine was not very successful in these cases. Because of this and the time element required for producing an active immune response by vaccine, the use of antirabies serum was introduced. Here specific antibodies preformed in a horse are passively supplied to the rabies-exposed patient so that they are available immediately. In fact, rabies represents an ideal situation for passive immunization by antiserum since we know not only the exact time of exposure but the exact point of introduction of the infecting agent.

While antiserum rapidly supplies antiviral antibodies, the effective

Table 2. *Indications and Recommendations for Postexposure Treatment of Rabies*

A. LOCAL TREATMENT OF WOUNDS INVOLVING POSSIBLE EXPOSURE TO RABIES

(1) **Recommended in All Exposures**

(*a*) *First-aid Treatment*

Immediate washing and flushing with soap and water, detergent or water alone (recommended procedure in all bite wounds including those unrelated to possible exposure to rabies).

(*b*) *Treatment by or under Direction of a Physician*

(i) Adequate cleansing of the wound.
(ii) Thorough treatment with 20% soap solution and/or the application of a quaternary ammonium compound or other substance of proven lethal effect on the rabies virus.[1]
(iii) Topical application of antirabies serum or its liquid or powdered globulin preparation (optional).
(iv) Administration, where indicated, of antitetanus procedures and of antibiotics and drugs to control infections other than rabies
(v) Suturing of wound not advised.

(2) **Additional Local Treatment for Severe Exposures Only**

(*a*) Topical application of antirabies serum or its liquid or powdered globulin preparation.
(*b*) Infiltration of antirabies serum around the wound.

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[1] Where soap has been used to clean wounds, all traces of it should be removed before the application of quaternary ammonium compounds because soap neutralizes the activity of such compounds.

Benzalkonium chloride, in a 1% concentration, has been demonstrated to be effective in the local treatment of wounds in guinea pigs infected with rabies virus. It should be noted that at this concentration quaternary ammonium compounds may exert a deleterious effect on tissues.

Compounds that have been demonstrated to have a specific lethal effect on rabies virus *in vitro* (different assay systems in mice) include the following.

Quaternary ammonium compounds

0.1% (1 : 1000) benzalkonium chloride = mixture of alkylbenzyldimethylammonium chlorides
0.1% (1 : 1000) cetrimonium bromide = hexadecyltrimethylammonium bromide
1.0% (1 : 100) Hyamine 2389 – mixture containing 40% of methyldodecylbenzyltrimethylammonium chloride and 10% of methyldodecylxylylene bis(trimethylammonium chloride)
1.0% (1 : 100) methyl benzethonium chloride = benzyldimethyl{2-{2-[*p*-(1,1,3,3 tetramethylbutyl)tolyloxy]ethoxy}ethyl}ammonium chloride
1.0% (1 : 100) benzethonium chloride – benzyldimethyl{2-[2-(*p*-1,1,3,3, tetramethylbutylphenoxy)ethoxy]ethyl}ammonium chloride
1.0% (1 : 100) SKF 11831 = *p*-phenylphenacylhexamethylenetetrammonium bromide

Other substances

43–70% ethanol; tincture of thiomersal; tincture of iodine and up to 0.01% (1 : 10,000) aqueous solutions of iodine; 1% to 2% soap solutions

B. SPECIFIC SYSTEMIC TREATMENT *(for footnotes see next page)*

NATURE OF EXPOSURE	STATUS OF BITING ANIMAL (IRRESPECTIVE OF WHETHER VACCINATED OR NOT)		RECOMMENDED TREATMENT
	At Time of Exposure	During Observation Period of Ten Days	
I. No lesions; indirect contact	Rabid	–	None
II. Licks:			
(1) unabraded skin	Rabid	–	None
(2) abraded skin, scratches and unabraded or abraded mucosa	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Start vaccine^1 at first signs of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Start vaccine immediately, stop treatment if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown		Start vaccine immediately
III. Bites:			
(1) mild exposure	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Start vaccine^{1,2} at first signs of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Start vaccine immediately, stop treatment if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown	–	Start vaccine^{1,2} immediately
	(*d*) wild (wolf, jackal, fox, bat, etc.)		Serum^2 immediately, followed by a course of vaccine^1
(2) severe exposure (multiple, or face, head, finger or neck bites)	(*a*) healthy	Clinical signs of rabies or proven rabid (laboratory)	Serum^2 immediately; start vaccine^1 at first sign of rabies in the biting animal
	(*b*) signs suggestive of rabies	Healthy	Serum^2 immediately, followed by vaccine; vaccine may be stopped if animal is normal on fifth day after exposure
	(*c*) rabid, escaped, killed or unknown	–	
	(*d*) wild (wolf, jackal, pariah dog, fox, bat, etc.)	–	Serum^2 immediately, followed by vaccine^1

level decreases with time after administration. Therefore, the combination of a single dose of antiserum with a full course of vaccine has been found most effective in postexposure prophylaxis of both experimental[5] and clinical rabies.[3] The antiserum provides antibodies early before the patient can respond to active immunization by vaccine, and the vaccine calls forth active immunity later when the antiserum effect is waning.[1]

However, in the course of studies on the most efficient schedules for this combined use of antiserum and vaccine, it was noted that under some conditions the antiserum interfered with the antigenicity of the vaccine.[2] This interference could be overcome by additional doses of vaccine and the present recommendation is for 21 daily doses of vaccine followed by single booster doses at 10 and 20 or more days after the last daily dose, whenever antiserum is used. In fact, the evidence is so convincing for more efficient, active, antiviral antibody production when booster doses of vaccine are inoculated, that even when vaccine is used without serum the booster doses should be given routinely.

There is no doubt that the combination of antiserum and vaccine is the most effective available means of postexposure prophylaxis. However, a course of vaccine alone appears to be adequate after mild types of exposure and in many rabies clinics the combined regimen is therefore limited to those severely exposed.

Vaccines

Even today, rabies vaccine is the crudest biological product given parenterally to man. Since Pasteur's day, vaccines for human use have been made from the central nervous system (CNS) tissue of infected animals—in this country from rabbits—and the virus attenuated or completely inactivated by one of a number of chemical or physical treatments. In more recent years it has been discovered that the rabies virus is not a strict neurotrope and is capable of growing in non-nervous system tissues. Thus, fairly good virus multiplication was found to occur in avian embryos.[7] In fact, the very effective live-virus vaccine for immunization of dogs which has been used throughout the world is made in chicken embryos.[8] Subsequently it was shown that rabies virus grown in duck embryos had a titer high enough to make a potent killed-virus vaccine.[9] Thus duck embryo killed-virus vaccine, which can be preserved in the dry state, is the most commonly used vaccine in this country today. It is still a crude tissue emulsion but has the advantage

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FOOTNOTES TO TABLE 2, B

[1] Practice varies concerning the volume of vaccine per dose and the number of doses recommended in a given situation. In general, the equivalent of at least 2 ml. of a 5 per cent tissue emulsion should be given subcutaneously daily for 14 consecutive days. Many laboratories use 20 to 30 doses in severe exposure. To ensure the production and maintenance of high levels of serum-neutralizing antibodies, booster doses should be given at 10 days and at 20 or more days following the last daily dose of vaccine in *all* cases. This is especially important if antirabies serum has been used, in order to overcome the interference effect.

[2] In all severe exposure and in all cases of unprovoked wild animal bites, antirabies serum or its globulin fractions together with vaccine should be employed. This is considered by the Committee as the *best* specific treatment available for the postexposure prophylaxis of rabies in man. Although experience indicates that vaccine alone is sufficient for mild exposures, there is no doubt that here also the combined serum-vaccine treatment will give the best protection. However, both the serum and the vaccine can cause deleterious reactions. Moreover, the combined therapy is more expensive; its use in mild exposures is therefore considered optional. As with vaccine alone, it is important to start combined serum and vaccine treatment as early as possible after exposure, but serum should still be used no matter what the time interval. Serum should be given in a single dose (40 IU per kg. of body weight) and the first dose of vaccine inoculated at the same time. Sensitivity to the serum must be determined before its administration.

over the older brain tissue type vaccine of being relatively low in its content of the nervous tissue antigen responsible for postvaccinal complications involving the CNS. By actual field experience it has produced such complications in a remarkably few instances. It also has a disadvantage – it is not as potent as average brain tissue vaccines, although of course it passes minimal potency test requirements and is effective in practice.

Recent research results along several lines suggest the possibility of future rabies vaccines in much more purified form. Rabies virus grows in tissue cultures including cultures of normal human cells.[12] Virus from brain tissue may be separated from tissue elements and concentrated to the point of being a practical source for vaccine.[11]

Reactions to Treatment. All patients receiving a course of vaccine will develop localized swelling, redness, and tenderness at the site of inoculation starting about the seventh dose. A rare individual may have an allergy to the tissue content of the vaccine, and, if so, a change should be made from duck embryo to rabbit brain vaccine or vice versa. The most serious complication is postvaccinal paralysis or encephalitis. If during the course of vaccine treatment constitutional effects such as headache, vomiting, fever, lymphadenopathy, or generalized rash develop, then vaccine should be stopped and the situation re-evaluated as to the desirability of further doses.

Antirabies serum is a horse serum product so negative skin tests for sensitivity are required before its use. It produces serum sickness in up to 30 per cent of those inoculated.

Indications for Specific Prophylaxis

The decision as to whether to use vaccine and antiserum is influenced by a number of facts in a given situation but many times these facts are unknown. If the biting animal remains clinically healthy for ten days then there has not been an exposure to rabies. The exception to this rule is a bat bite. Here all cases should be treated no matter what the clinical condition of the bat. Laboratory diagnosis of the biting animal is important but the search for the presence or absence of rabies virus in the salivary glands as well as the brain should be emphasized. Table 2, reprinted from the World Health Organization Expert Panel on Rabies Report,[13] covers most possible situations of exposure and gives the indicated treatment.

PRE-EXPOSURE PROPHYLAXIS

In certain occupational groups such as veterinarians, dog-handlers, and mailmen where there is repeated exposure to animal bites, it is often wise to immunize against rabies before exposure. Certainly immunity already established at the time of exposure is more efficient in preventing the disease than that induced after the exposure.

The regimen recommended here is two doses of vaccine one month apart followed by a booster dose four to six months later. To be certain that an immunological reaction has taken place, the patient should be bled one month after the booster dose and the serum tested for antirabies antibodies. If they are not demonstrable, additional booster doses should be tried. If antibodies are demonstrated, a booster dose should be given every one to three years. On subsequent exposure, it is recommended that a single dose of vaccine be given in the case of mild exposure and five daily doses plus a booster dose at least 20 days later for severe types of exposure.

SUMMARY

Rabies in wildlife, especially in foxes, skunks, and bats, is a more important source of exposure of man in the United States than that in domestic species, including the dog. The best postexposure prophylaxis of rabies in man is the combination of one dose of antirabies serum followed by 21 daily doses of vaccine, plus booster doses of vaccine at 10 and 20 or more days after the last daily dose.

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Postinfectious and Vaccinal Encephalitis

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For many years the concept of a postinfectious and postvaccinal type of encephalitis as distinct from a viral encephalitis has been well established. The criteria for making this differentiation can be summarized as follows: (1) central nervous system illness occurring usually as the original illness is subsiding, (2) pathological changes characterized by perivenous demyelination and/or microglial reaction involving the white more than the gray matter, (3) failure to isolate the agent responsible for the initial illness from the nervous tissue despite adequate technical procedures.

However, an increasing number of patients have been reported as dying from a neurologic complication occurring at the correct time after an initial illness and differing little, if any, from other patients in their clinical manifestations, whose brains failed to show the characteristic pathology. The pathologic changes in these brains were nonspecific. The pathology of these two types will be illustrated first, as being the basis on which a final diagnosis depends. The clinical and epidemiologic features of the neurologic illnesses following certain types of immunization (smallpox, rabies, and others) and various exanthems (measles, German measles, varicella, variola) and mumps will then be summarized and related to the pathologic findings.

PATHOLOGY

The lesions characteristic of post- or para-infectious encephalopathy are around small veins mainly in the white matter. Early there is an infiltration of cells concentrically arranged in an area largely outside the Virchow-Robin spaces, although these may contain a few cells. The margins of the lesions are ill defined as the infiltrating cells become sparser. Myelin stains show degeneration of myelin sheaths in these areas which, with time, become clearly and sharply outlined. (Fig. 1) The axon cylinders are intact and the neurons in the area show minor changes, if any. If the lesion is more acute, hemorrhages occur about the veins in addition to the changes just described. When such changes

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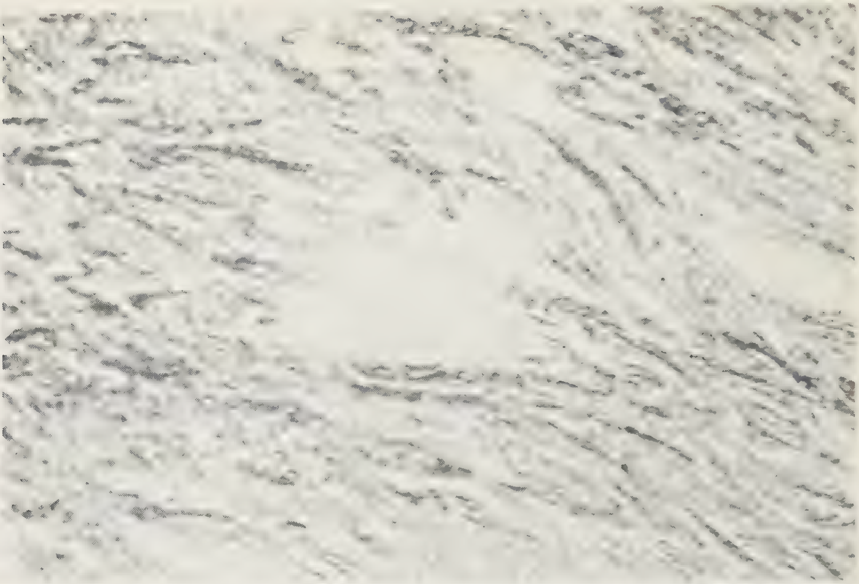

Figure 1. Myelin stain showing sharp area of demyelination about two veins.

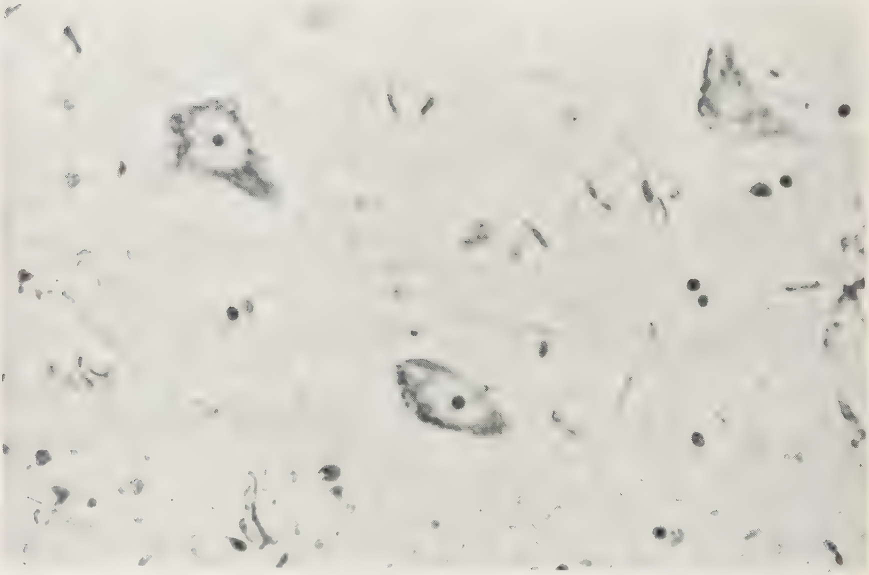

Figure 2. Normal neuron (H & E stain).

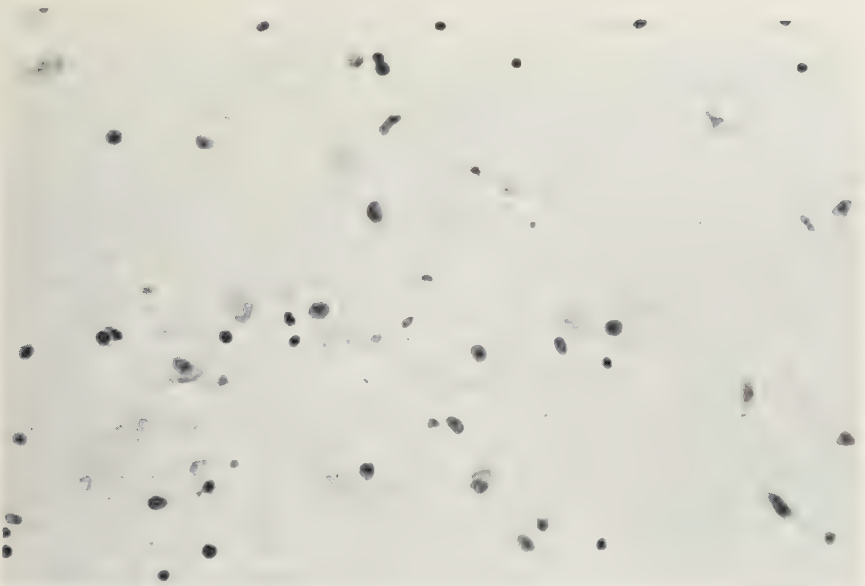

Figure 3. Vacuolated neurons in cortex of a patient with anoxic encephalopathy (H & E stain).

are present, the pathologic diagnosis of acute hemorrhagic leukoencephalitis is made.

In contrast to these findings there is, in some patients dying with the premortem diagnosis of postinfectious encephalitis, a series of nonspecific changes such as are found in anoxia. These consist of edema, acute degeneration, and vacuolization of the neurons mainly in the cortex (Figs. 2, 3) and no accompanying demyelination. This type of pathologic change is also found in an ill-defined group of cases recently described by Lyons et al.[17] as "acute encephalopathies of obscure origin" which are associated with acute upper respiratory infections, influenza, and gastroenteritis. In the brains of certain individuals dying of postinfectious encephalitis, pathologic changes of both types are found, characteristic perivenous demyelination in some areas, and nonspecific changes of the neurons in others. This may be an indication that the nervous system was responding to more than one noxious factor. Direct viral infection results in changes that differ from both of these, namely destruction of neurons with or without the development of characteristic inclusion bodies, and intense infiltration of Virchow-Robin spaces with cells.[25]

CLINICAL AND EPIDEMIOLOGIC CHARACTERISTICS

The significance of this group of illnesses in the United States can be seen from Table 1. There appears to be little variation over the years from an average of about 30 per cent of the total number of encephalitides reported.

Postvaccination Neurologic Reactions

These have been described after a number of immunizations, particularly smallpox and rabies.

Table 1. *Postinfectious and Postvaccination Encephalitis as Per Cent of Total Encephalitis in U.S.A.*

	1962 (52 wks.)		1965 (35 wks.)	1966 (35 wks.)
Mumps	14.8	33.9	31.9	30.9
Measles	14.0			
Varicella	3.2			
Influenza	1.6			
Postvaccinial	0.3			
Other	8.2	65.1	68.1	69.1
Arbo	11.2			
Unknown	46.7			
Total Cases	2,410		1,657	1,846

From Morbidity and Mortality Reports, U.S. Dept. of Health, Education and Welfare.

SMALLPOX VACCINATION. This complication did not become clearly recognized until 1922[42] when, in Great Britain, 11 fatalities were reported. Prior to this time neurological deaths were rare. From 1853 to 1896 the complications of generalized vaccinia and convulsions in infants during the febrile phase were recognized, but nothing resembling the condition we now call postvaccinal encephalitis was reported, despite the excellence of the clinical observations of that time and the vigilance of a rabid group of antivaccinationists. The committees on vaccination in 1928 and 1931[54, 55] established that the entity existed and that it was not due to poliomyelitis or encephalitis lethargica. At the same time other reports from Germany, Holland, and Austria revealed the appearance of similar cases. Turnbull and McIntosh[67] reported the pathological findings in detail, emphasizing the wide areas of perivenous demyelination in the white matter. They demonstrated the presence of vaccinia virus in two of seven brains. The ability to demonstrate virus in such cases is exceptional despite vigorous efforts directed to this end,[68] and suggests contamination from the blood as was noted by Angulo et al.,[3] who also reported a positive isolation. In this patient the vaccination site was described as appearing "necrotic" at time of death on the eleventh day, suggesting a "progressive vaccinia" with a persistent viremia. As these authors also emphasized, the pathologic finding of perivenous demyelination found in all these brains was unlike that caused by a direct vaccinia viral infection in animals in which the myelin sheaths are unaffected.[32]

The incidence of this complication varies markedly from country to country, as reviewed by Larbre et al.[40] (Fig. 4). In New York City during the smallpox scare in 1947, the proven incidence was less than 1:100,000.[21] There appears to be no adequate explanation for this variation and it has been clearly proved that the results are not due to the vaccine employed, since there has been no correlation of the incidence of encephalitis with the source, the neurotropism, or the antigenicity of the virus in the vaccine.[68]

Until recently, it had been assumed that all patients diagnosed as suffering from "postvaccinal encephalitis" belonged in one clinical and pathological category. However, in 1960 DeVries[16] pointed out that the patients should be divided into two groups according to the pathologic changes found in the nervous system. In one group the characteristic perivenous demyelination was found, whereas the other

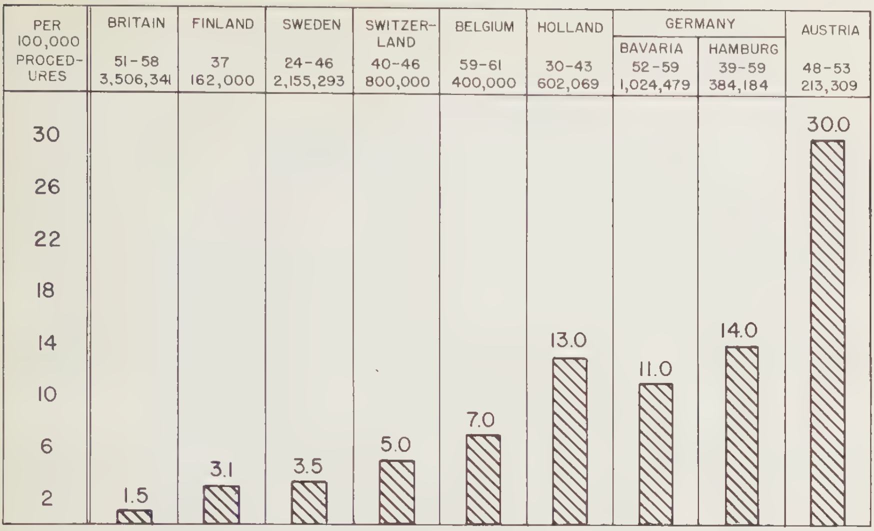

Figure 4. Graph of incidence of postvaccinal encephalitis in different countries. (From Larbre et al., Arch. franc. de Pediatrie *21*:595, 1964.)

group manifested various nonspecific changes without demyelination. He suggested reserving the term "encephalitis" for the former and classifying the latter as postvaccinal "encephalopathy" (Table 2). These two groups can sometimes be distinguished clinically by the age of the patient, the incubation period and the type of onset (Table 3). Below the age of two years, all of the pathologic changes have been reported as of the nonspecific type and the true encephalitis as occurring only above this age. However, patients with "encephalopathy" can also be found in the older age group. The incubation period is more variable in the encephalopathic group, the true "encephalitis" occurring strictly

Table 2. *Post-Smallpox Vaccination Encephalitis: Pathological Changes*

"Encephalitis"	Perivenous demyelination (microglial) Little edema or destruction of neurons
"Encephalopathy"	Edema, vacuolization of neurons

Table 3. *Post-Smallpox Vaccination Encephalitis: Clinical Features*

	< 2 yrs.	>2 yrs.
Onset	Explosive with convulsion	Rapid and progressive
Coma	Rapid onset	Variable
CSF	Usually normal	Variable
Cord involvement	No	Yes
Incubation	2 to 18 days	8 to 15 days
Pathology	Nonspecific	Perivenous microglial reaction and demyelination.

Table 4. *Post-Smallpox Vaccination Encephalitis: Incidence per 100,000 Procedures*

AGE (yrs.)	PRIMARY		REVACCINATION	
	Cases	Deaths	Cases	Deaths
0– 1	1.6	0.9	0	0
1– 4	0.2	0	0	0
5–14	1.8	0	1.2	0
15 and over	2.9	0.3	0.8	0.2

Modified from Griffiths, England and Wales, 1951–57.

Table 5. *Post-Smallpox Vaccination Encephalitis: Prophylaxis*

Age of vaccination	2nd year
State of individual	Absence of other illness
Use of antivaccinial immune gamma globulin (AGG)	Areas of high incidence
Use of killed vaccine	Being explored

between the eighth and fifteenth days. An explosive onset with convulsions is more typical of the encephalopathic group.[16]

The case fatality figure for postvaccinal encephalitis have been stated to be as high as 30 per cent.[52] However, these figures have not taken into consideration the separation into the two groups just described. On the basis of the high death rate noted by Lyons et al.[47] for the group of acute encephalopathies with pathologic changes in the brain of a similar nature, it is suspected that this rate may be high in those infants under two years of age who respond similarly to smallpox vaccination. Again, since the analyses prior to 1964 have been made without making this clinicopathologic differentiation, the death rate from true postvaccination encephalitis may be lower than has been quoted. In the series reported by Spillane and Wells[66] in 1964, this differentiation was made. They described 14 patients among 800,000 vaccinees during a mass vaccination campaign in Wales, 11 being diagnosed as "encephalitis" with one death and three, among older children, as "encephalopathy" with no deaths.

Other features of this complication are shown in Table 4, namely that prior vaccination appears to be favorable in preventing this complication except when there is a long interval between the two procedures and there is a higher incidence of neurologic complications in the first year than in the 1–4 age group. This latter conclusion is open to dispute since other statistics reviewed by Larbre et al.[40] indicate that the first six months of life is the safest period. A possible benign form of postvaccinal encephalopathy has been reported[30] which was manifested by severe prolonged convulsions, unassociated with fever, in infants under two years of age, 7 to 10 days after vaccination. Trismus was a common finding in these; other authors have noted trismus in postvaccinal encephalitis as well as other types of severe encephalopathy.[27]

In regard to prophylaxis, Table 5 indicates some of the points. (1) The recommended age of vaccination in U.S.A. and Great Britain is now, officially, sometime during the second year of life.[14, 72] (2) A careful consideration of the state of the individual is important, since it is good sense to postpone vaccination if there is the slightest doubt about the child being completely healthy or if there is a history of previous neurologic symptoms. (3) The efficacy of an injection of antivaccinial immune gamma globulin (AGG) at a different site simultaneously with the vaccination has been statistically shown by Nanning[56] in Holland. Among 53,630 Dutch recruits given 2 ml. of AGG, there were three cases of encephalitis with one death while there were 13 cases of encephalitis, with one death, among 53,044 who received a placebo in place of the AGG; an incidence of 1:4000, the characteristic high rate found among recruits into Dutch armed services. (4) It has been suggested that initial immunization with a killed vaccine might prevent the viremia and thus initial damage to the brain cells and release of antigens of neural origin. At present this possibility is being explored but no good evidence has as yet been produced in favor of this procedure.[35] Since the neurologic complications under two years of age do not seem to be of the autoimmune variety, it seems doubtful that this procedure would have a place in the vaccination of infants.

RABIES. Joseph Meister, who was vaccinated by Pasteur in 1885 with the first antirabies vaccine, developed a local and generalized reaction but fortunately not a neurologic complication or the vaccine might have been abandoned.[8] However, since then, many neurologic complications have been reported. The incidence of this complication has varied considerably (see Table 6). Greenwood's analysis of 1,290,758 vaccinees in 1945 revealed an incidence of paralytic accidents from all types of neural vaccine as 1 in 5,187 with a case fatality rate of 25 per cent. The rate has varied with the type of vaccine and the number of inoculations. It is well to point out that this complication has been reported[59] following the use of duck-embryo vaccine although the incidence appears to be much lower than with the cord-derived vaccines. The types of reaction which are encountered are summarized in Table 7.

Table 6. *Post-Rabies Vaccination Encephalitis: Incidence*

CONDITIONS	REACTIONS
Neural vaccine	1/300* to 1/7000†
Non-neural vaccine	1/50,000‡
< 7 injections	+§
> 14 injections	+++++§
Prior vaccination	Increased risk?

*Blatt and Lepper.
†Sellers, T. F.: J.M.A. Georgia 36:30, 1947.
‡Prussin and Katabi.
§Applebaum et al.

Table 7. *Post-Rabies Vaccination Encephalitis: Clinical Features*

Meningeal reaction
Peripheral neuritis:
  (a) individual nerves; e.g., facial palsy
  (b) extensive polyneuritis with a Guillain-Barré-Landry type of reaction
Encephalitis
Dorsolumbar myelitis
Signs of increased intracranial pressure

Case fatality	25%*
Sequelae	36% (mild)†

*Based on 222 cases analyzed by Greenwood.
†Based on 46 cases analyzed by Applebaum et al.

Functional recovery is usually complete although slight motor weakness, sensory disturbances, ataxia and difficulty with bladder control may remain,[8] especially following dorsolumbar myelitis.

OTHER. Rarely neurological complications are reported after *vaccination against pertussis*. The incidence of this reaction is undeterminable but certainly very low. However, such incidents do occur usually within hours of receiving the vaccine. In the British whooping cough vaccine trials, 14 of 46,000 children had a convulsion within 72 hours of being vaccinated (1:3,300), but no severe case of encephalitis was reported.[13] Berg,[7] in a review of 107 cases reported up to 1958, found no relation to age or dosage and only in very few was there a suggestive history of allergy. Characteristically the onset is rapid and the consequences serious. Eight children in his series died and only 50 per cent recovered completely. Encephalopathy occurs also after an attack of pertussis and Litvak et al.[44] reported an incidence of 1:125 cases in children admitted to the hospital with severe pertussis. In both instances the pathology is characterized by nonspecific findings such as congestion, edema, and petechial hemorrhages; there are no perivascular or perineuronal collections of inflammatory cells or perivenous demyelination.

Encephalopathy has also been reported after *vaccination with polyvalent influenza vaccine*;[71] and after *yellow fever vaccination* in infants under six months.[21] It seems probable that, in the latter instance, the infant brain is especially liable to direct infection by the neurotropic yellow fever virus since viremia occurs after inoculation of this attenuated but live neuroadapted virus.[70] Peripheral neuritis, either single or generalized, encephalomyelitis, and focal encephalopathy have been reported after the use of *tetanus antitoxin* of animal origin.[58]

Postinfectious Neurologic Complications

MEASLES. Of the postexanthem encephalitides being considered, the most frequent and most serious is that of measles. The earliest clinical description appears to be that of Lucas[46] who, in 1790, gave a vivid description of a 23-year-old woman who developed symptoms and signs suggesting transverse myelitis, on the sixth day after the appearance of the rash. With commendable restraint, Lucas avoided the drastic therapy common to that age and she recovered from this attack; further history revealed that she had had a similar experience, following variola, nine years previously. She would perhaps fall into the group of patients with recurrent encephalitis as described by Alcock et al.[2] These authors suggested that one neurologic insult increased the susceptibility of the brain to another. The incidence of measles encephalitis varies in different studies; 1:1000 cases is about the average in U.S.A. but has been reported as high as 1:642[28] (Table 8). Ehrengut[20] points out the low incidence of neurologic complications in children under two years (1:14,158). He quotes Fiedler as stating that typical microglial encephalitis does not occur in this age group. The neurologic complications that do occur among infants appear to resemble pathologically the encephalopathies found with smallpox vaccination. The highest incidence in his series was 1:2,558 in the group over ten years old in whom the pathologic picture was that of perivenous demyelination. The relatively low incidence in this German report supports Von Magnus's comment[69] that complications of measles appear to be fewer in Europe than in the United States.

The clinical features shown in Table 9 are taken from a study by Boughton[11] of 168 patients admitted to the infectious disease hospital in Sydney, Australia from 1942 to 1959. The multiplicity of neurologic signs is obvious: Cranial nerve palsy, affecting most frequently the eye, was common, while facial palsy was the next most frequent. Hemiplegia occurred in 10 per cent and other paralyses were noted. The serious prognostic significance of transverse myelitis is seen; 7 of 13 patients showing residual signs. Tonic spasm of the arms probably indicating decorticate rigidity was a serious sign among these patients since all three died. Table 10 reviews some other aspects of the disease. The time of onset is characteristically when the patient appears to be recovering and the temperature has subsided, only to rise again with the onset of this complication. However, on rare occasions neurologic manifestations can precede the onset of the rash by as long as ten days.[31]

The findings in the cerebrospinal fluid (CSF) are important in that no pleocytosis occurs in as many as 60 per cent of patients. On the

Table 8. *Postmeasles Encephalitis*

CONDITIONS	REACTIONS	
Different epidemics	1/1000*	
Age 0– 4 yrs.	1/14,158†	
5– 9 yrs.	1/5,502†	
> 10 yrs.	1/2558†	
Severity of illness	No relation	
Day of rash	Peak 4th to 5th	
Case fatality	9%‡	22%§
Sequelae	23%	34%‖

*Varies with epidemics, most frequent figure in the U.S.A.
†Ehrengut (1965).
‡Boughton (1964) analysis of 168 patients.
§Miller et al. (1956) analysis of 579 patients.
‖Miller et al. (1956) analysis of 178 patients.

Table 9. *Postmeasles Encephalitis: Clinical Features of 168 Patients**

	NUMBER	RESIDUAL	
		Transient	Permanent
Cranial nerves (various)	42	33	3
Hemiplegia	16	10	6
Monoplegia	6	2	4
Paraplegia†	21	10	11
General hypotonia	20	18	2
General spasticity	14	9	5
Spastic legs, flaccid arms	4	2	2
Arms, tonic spasm	3	3	–
Urine retention	22	22	–
Others‡	20	6	14
TOTAL	168	115	47

*Boughton (1964).
†Thirteen with transverse myelitis, 7 with permanent residual.
‡One with Guillain-Barré, 7 with permanent dementia.

Table 10. *Postmeasles Encephalitis: Clinical Features* (Continued)*

Onset	1. Sudden convulsions, fever → coma 2. Fever, headache, vomiting, behavior change, delirium → stupor → coma
Peak of onset after rash	5 days (−10 to 24)
CSF pleocytosis	85%,‡ 40%,* 43%†
Protein raised	47%‡

* Miller et al. (1956).
† Boughton (1964).
‡ LaBoccetta et al.

other hand, pleocytosis greater than 10 cells/cu. mm. may be found in the spinal fluid of patients without clinical evidence of central nervous system involvement, as shown by Ojala[57] (8 per cent of 123 patients) and Cronemeyer[15] (4 per cent of 70 patients). The pleocytosis in these uncomplicated cases was most likely to be found between the fifth and tenth days and in a single patient in each series the cell count was over 100 cells/cu. mm. It is worth noting that high values (greater than 75 mg. per cent) for sugar have been recorded, on occasion, in patients in coma, with or without convulsions.[39] CSF protein is elevated in about one-half of the patients, but there appears to be no correlation between elevated protein and pleocytosis in the spinal fluid since either one can be present without the other.[53] In the analysis by Miller et al.[53] of 579 cases reported in the literature to 1955, the case fatality was 22 per cent.

The onset of this complication apparently has no relationship to the severity of the initial illness; it has been described following measles modified by prior injection of gamma globulin[6] and, extremely rarely, after vaccination with Edmonston or the Schwartz strains (9 among approximately 6 million vaccinees in 1965) without deaths or reported sequelae.[51]

The prognosis is extremely uncertain in any given patient. Among 288 patients analyzed by Miller et al.,[53] coma and convulsions were found more often among the patients who died than those who survived; survival for one week greatly improved the outlook for eventual survival. The duration of coma is apparently not related to the occurrence of sequelae; complete recovery can occur even after prolonged coma. The incidence of sequelae varies in different series and with the length of time after the illness for which the patients are examined. Miller et al.[53] in 1956 noted that 34 per cent of 178 patients gathered from the literature had residual neurologic deficits, approximately half of these being major. Almost two-thirds of these patients had serious intellectual deficit and/or behavior disorders. In Boughton's large series of 168 patients, there was a case fatality rate of only 9 per cent and permanent residuals occurred in 23 per cent. Transient psychological changes are quite often seen which may disappear shortly in a permissive environment. Prolonged follow-up over years reveals a better eventual prognosis in many patients who appeared at one time to be permanently damaged, while, on the contrary, children who appear to have recovered completely demonstrate learning difficulties later in school.

The isolation of measles virus has been reported only twice, once from the brain, by Shaffer et al.[64] in 1942, and once from the spinal fluid of a patient who recovered, by Lopes Fernandez et al. in 1947.[45] In both these instances the virus was isolated in Macacus rhesus monkeys, now known to be extremely susceptible to infection by measles spontaneously after a short while in captivity. Despite technical competence, other attempts have failed. The relationship of the virus to the clinical illness will be discussed after reviewing neurologic complications of other infections.

VARICELLA (*Chickenpox*). Encephalitis following varicella is very infrequent but no quantitative estimates are available. The onset appears, as in measles, after the rash develops. In addition to encephalitis, polyneuritis and myelitis occur even more rarely. The clinical features do not differ essentially from those found in measles encephalitis, but the relative frequency of certain features differs widely in the two diseases, as can be seen from the analysis of Miller et al.[53] Coma, hemiplegia, and extensor plantar response were common in measles, 45, 12, and 71 per cent respectively, as opposed to 19, 3, and 28 per cent respectively in varicella. Cerebellar ataxia, on the other hand, was much more frequently seen in the postvaricella encephalitis, 34 per cent as contrasted with 10 per cent in that following measles. The usual pathologic picture in varicella encephalitis is identical with that of measles. A persistent focal encephalitis in the hypothalamus has been described in which the patient died of a hypothalamic syndrome 14 months after varicella with pneumonia.[43] No attempt was made to isolate virus from the brains of two patients dying of varicella on the seventeenth and the fourth day respectively although virus was isolated from the blood. The brains were histologically normal.

A different pathologic picture may also be seen resembling that of postvaccinal "encephalopathy" with edema and acute neuronal damage without demyelination, as exemplified in a patient dying at Philadelphia General Hospital.[61] This was accompanied by the findings of acute fatty degeneration of the liver. A similar combination can be noted in the description by Blair et al.[9] of a patient dying in England. The combination of encephalopathy and fatty liver is probably quite nonspecific since it has been described in a patient from whose brain reovirus Type I was isolated[33] and in another from whose liver adenovirus Type III was recovered,[19] and in a number of patients in whom no etiology was diagnosable.[23, 60]

VARIOLA (*Smallpox*). Neurological complications of smallpox were described as early as 1724 by Clifton (quoted by Greenfield[25]). In a review of 13,686 patients with mild smallpox, Marsden[49] identified eight with encephalitis, 1:2000. Four of these died and their brains revealed the typical perivenous demyelination. DeVries[17] reviewed the pathology of eight other patients and reported that they were examples of perivenous demyelination. He comments that this complication occurs only with mild and not severe smallpox.

RUBELLA. Rubella must be considered somewhat separately from the other exanthems in that it occurs in two forms, congenital and acquired. The congenital form, caused by intrauterine infection, is a manifestation of persistent infection, and virus can always be isolated from the brain as well as other organs. The pathologic picture, as recently described in detail by Rorke and Spiro,[62] is characterized by a widespread cerebrovascular degeneration. The vessel walls contain amorphous, condensed granular material which seems to be a protein

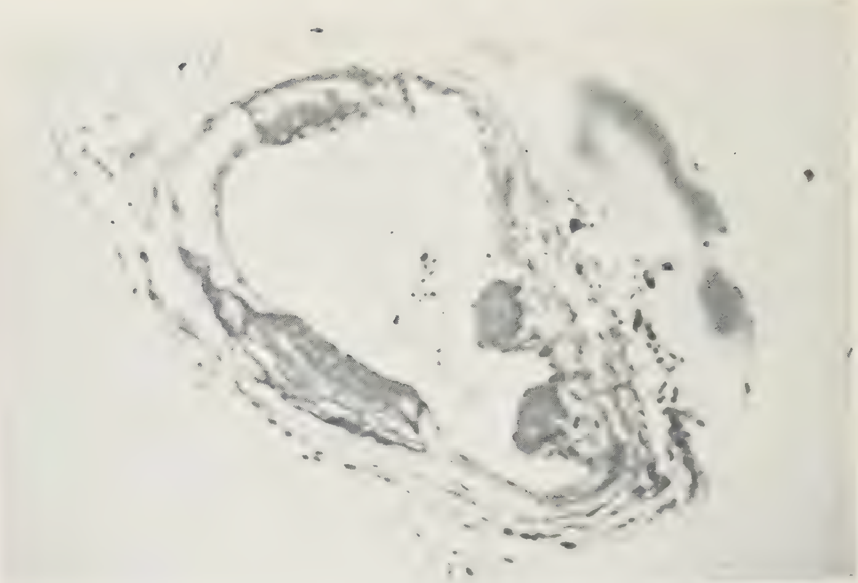

Figure 5. Vessel from the brain of congenital rubella encephalitis stained to show mucopolysaccharide in the wall (PAS stain). (From Rorke and Spiro, J. Pediatrics 70:243, 1967. The C. V. Mosby Co., St. Louis.)

Table 11. *Postrubella Encephalitis*

Incidence		1:5000[*]	1:4,300[†]
Case fatality		20%	
Peak onset after rash		4 days (−9 to 11)	
	Clinical Features[‡]		
Convulsions	57%	Tremors, athetoid	17%
Stupor	15%	CSF pleocytosis	70%
Coma	52%	Sequelae	±5%
Ataxia	14%		

[*] Margolis et al. (1942).
[†] Kenney et al. (1965).
[‡] Miller et al. (1956).

mucopolysaccharide complex (Fig. 5). Associated with the damaged vessels are foci of tissue necrosis. There is also delay in myelin formation without axis cylinder damage. In the acquired type the clinical picture is similar to that of measles (see Table 11). The incidence has been reported as approximately 1:5000 during two epidemics. The case fatality is as high or higher than that in measles but residual deficits appear to be very rare. The pathology in the few patients dying of this complication appears to differ from that of measles and varicella in that characteristic perivenous demyelination is exceptional, being noted in only two of nine case reports reviewed by Miller et al.[53] and in none of the three patients reported by Sherman et al.[65] In the majority of the patients only nonspecific changes of edema, microscopic hemorrhages, some perivascular cuffing, and occasional neuronal damage was described, this being the picture of "encephalopathy" as described earlier. Because most of the patients died within 72 hours after onset of the neurologic symptoms, Miller et al.[53] speculated that these pathologic changes were early manifestations which in time would progress to show typical demyelination. That this is extremely unlikely is attested to by the observations of DeVries[16] that typical demyelination was present in the brains of those dying after smallpox vaccination within 24 to 48 hours after onset of symptoms.

Mumps. The neurologic complications of mumps must be separated clinically into those in which the main manifestation is meningeal and those presenting with the picture of encephalitis. The former is common, with an incidence reported as high as 30 per cent.[5] It probably represents the direct invasion of the central nervous system by the virus, since the virus has been isolated from the spinal fluid.[29] It may appear before or in absence of parotitis and the course is short and benign. The cerebrospinal fluid shows a lymphocytic pleocytosis that may reach 1000 cells/cu. mm. It occurs five times as frequently in males as in females. Since pleocytosis of six cells and over per cubic millimeter may occur in 51 per cent of patients with uncomplicated mumps, many showing 100 to 300 cells/cu. mm.,[5] the diagnosis must depend on the concomitant symptoms and signs.

True encephalitis is much less common, and the data are hard to assess although Russell and Donald[63] in 1958 reported an incidence of 1:6000. The clinical features do not differ significantly from those described in some detail under measles (see Table 9). The case fatality reported by Miller et al.[53] was 22 per cent among 27 cases, serious sequelae being found in 7 of the 21 survivors (33 per cent). The pathology in 20 reported cases, as reviewed by Donohue et al.,[18] does not differ from that of measles; namely, a perivenous demyelination is the characteristic feature.

MECHANISM OF POSTINFECTIOUS ENCEPHALITIS

In his review of the problem in measles, Koprowski[38] proposed the allergic hypothesis for the nervous system damage, comparable to experimental allergic encephalitis of animals. He emphasized the paucity of reports on attempts at virus isolation and suggested that this was due to the lack of success despite technologic competence. The rarity of virus isolation from the brain in vaccinia and in the other infections reviewed has been commented upon. This does not mean that the virus has had no part in the pathogenicity of this group of diseases. On the contrary it seems probable that, during the initial viremia, virus does infect brain cells, but due to the presence of antibodies or state of the virus in the cell, no isolation of infective virus is possible as a rule. In support of this, two suggestive observations have been made in regard to measles, which probably can be extrapolated to those other infections that are accompanied by encephalitis. The first is that of Gibbs et al.[22] who demonstrated that electroencephalographic changes were consistently found in apparently uncomplicated measles, and the second that of Adams et al.,[1] who found inclusion bodies histologically in the brain of 15 of 20 patients dying of postmeasles encephalitis. These inclusion bodies, either only cytoplasmic or both cytoplasmic and intranuclear, were in the cells of the meningeal infiltration and the cells infiltrating perivenously. They were indistinguishable in appearance from the inclusions found in the lungs of patients dying of measles and in the brains of hamsters dying of infection by a neurotropic strain of measles virus. Although no virus was isolated from the spinal fluids of 40 such patients or from the brains of three patients despite adequate technical procedures, the histological evidence of the presence of virus is very convincing. The cells damaged by such an initial viral infection could leak altered cell protein into the blood stream which could stimulate immunologically competent cells as they coursed through the brain capillaries. The antibody produced by these cells could react with the host's neurologic system, producing the myelin destruction characteristic of this group of diseases which is identical with the lesions of experimental allergic encephalitis produced in animals by inoculation of heterologous or even autologous brain tissue.[34]

SUMMARY

Approximately one-third of cases clinically diagnosed as encephalitis in the United States follow vaccination or a recognized infectious disease.

The incidence, case fatality rates, and sequelae vary with the antecedent illness or procedure and, even within a single entity, from country to country. The variability of the clinical features presented by this group of patients has been indicated in the tabulations. A more descriptive analysis of illustrative patients has been prepared by Kennedy and Wanglee.[36]

The pathology of the brains of most of those who die is identical with that of experimental allergic encephalopathy produced by the injection of brain tissue into animals. This resemblance and the usual failure to isolate the virus of the associated illness from the brain has supported the concept that these complications are the result of an autoimmune process following destruction of brain cells during the initial viremia.

Despite the characteristic appearance of perivenous demyelination in the brains of most of these patients, to which may be applied the term "encephalitis," some, apparently identical, present only nonspecific changes of edema and neuronal swelling and degeneration, to which the term "encephalopathy" may be applied. A third group has typical perivenous demyelination in some areas while in others nonspecific findings are present. Clinically, it is often not possible during life to determine what pathologic changes are taking place in any given patient. However, in patients under two years of age "encephalopathy" is the rule. In older patients the clinician may be steered towards a diagnosis of "encephalopathy" rather than "encephalitis" if the onset is explosive with convulsions or if, in the case of vaccinia, the onset occurs outside the limits of the second week after vaccination.

The striking lack of correlation between the occurrence of these complications and the severity of the inciting disease suggests that the host and not the parasite is the major factor in the reaction.

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Sulfonamide-Resistant Meningococcal Disease

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Meningococcal disease is not a cause of high morbidity or mortality when compared to other communicable diseases in recent years. Instead, the meningococcus relies for its notoriety upon its awesome and dramatic ability to cause death in a remarkably short period of time. Indeed, compared to the number of unapparent infections, the number of cases of disease caused by this pathogen are very few. These cases, in interepidemic periods, remain a cause of anxiety to pediatricians, military surgeons, and physicians dealing with closed populations. More recently this concern has heightened because of the appearance of sulfonamide-resistant strains of meningococci. The pattern of sulfonamide-resistant meningococcal disease and its treatment and behavior with prophylactic measures are the subject of this paper.

From time to time meningococcal disease becomes widespread throughout the world, as in 1805, 1837, 1854, 1876, 1898, and during the two World Wars. It has become axiomatic that these widespread outbreaks were caused primarily by the Group A meningococci. As a corollary, between epidemics cases were usually caused by serotype Group B, C, and D organisms and occurred either singly or in small, seemingly unrelated, outbreaks. With the advent of sulfonamides in the late 1930's and early 1940's, treatment of the disease reduced case fatality rates from 40 to 65 per cent to around 15 per cent.[17] The use of sulfadiazine as a chemoprophylactic agent was advanced during World War II when it was noted that 2 gm. of the drug a day for two consecutive days administered to a closed population would cause cessation of cases during an outbreak. The medical profession relaxed, secure with the sulfonamides and the newer antibiotics, but was rudely awakened in 1963 when it was demonstrated in several military installations that meningococcal cases continued in spite of repeated installation-wide programs of the administration of sulfadiazine.[25] The following year another circumscribed military epidemic in which sulfonamide-resistant bacteria were isolated occurred at Fort Ord, California. The almost hysterical publicity that resulted ended only with the temporary closing of Fort Ord as a training center, a measure that reduced the occurrence

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Table 1. *Serotype and Sulfadiazine Sensitivity of Meningococci Found in U.S. Army Training Centers (Jan. 1964 to 24 May, 1966)*

SEROTYPE	1964		1965		1966		TOTALS	
	Res.	Sen.	Res.	Sen.	Res.	Sen.	Res.	Sen.
B	163	78	77	46	115	39	355	163
Bo*	1	4	4	3	1	5	6	12
C	1	23	1	13	6	10	8	46
NT†	1	3	0	1	1	2	2	6
TOTALS	166	108	82	63	123	56	371	227

*Serotype Boshard, analogous to Slatterus Type Y
†Nontypable
Res., resistant; Sen., sensitive

of cases for almost a year. These two outbreaks brought three aspects of the presently occurring disease to our attention: first, that mass chemoprophylaxis was no longer an assured method for controlling meningococcal disease; second, that sulfonamide-resistant Group B meningococci were causing the majority of clinical disease; and, third, that there was an increased incidence of meningococcal disease in the civil population caused by the same sulfonamide-resistant Group B organisms.[20]

The Public Health Service has reported resistant Group B and C isolates from widespread areas in the United States civilian population. Walker and Strom[35] alerted the clinicians of Minneapolis of the presence of a highly resistant Group C case in that city. In 1965, five of nine cases of meningococcal meningitis in U.S. Armed Forces and their dependents in Europe were due to Group C organisms that were resistant to 0.1 mg. per 100 ml. of sulfadiazine.[5] The 1965 annual report from the Walter Reed Army Institute of Research also pointed out that "sulfa-resistant Group C strains began to appear in significant numbers" (at Ft. Dix, New Jersey).[34] Groups B and C resistant meningococci from cases were reported from Alaska,[28] Africa, and Western Europe in 1964 and 1965.[14] In retrospect, Feldman reported evidence that partial sulfonamide resistance, defined as growth in media containing 0.1 mg. per 100 ml. of sulfadiazine, had been present in one Group B strain in 1937.[12] Studies in 1948[31] and 1954[23] on susceptibility of meningococci to sulfadiazine revealed moderate resistance was present even in those years. More recently, Dr. Feldman[13] reported 55 of 109 Group B strains of meningococci from civilian cases to be resistant to 1 mg. per 100 ml. of sulfadiazine. Table 1 lists meningococcal isolates from a portion of this disease in the U.S. Army during the past three years.[33]

In summary, since World War II, strains of sulfonamide-resistant meningococci have been building up in the United States. At present the major portion of meningococcal disease is caused by Group B sulfonamide-resistant meningococci.

Information on the true prevalence of meningococcal infection in the general population at any single time is not available. Some investigators have sampled essentially closed populations to determine carrier rates during periods of high disease incidence. They have been handicapped by the inability to measure immunologic response to

Table 2. *Meningococcal Carrier Studies in Inductees (of Less Than 24 Hours), 1964 to 1966**

	NUMBER TESTED	NUMBER INFECTED	PER CENT INFECTED
Ft. Ord, Calif.	3204	672	20.9
Ft. Leonard Wood, Mo.	370	87	23.5
Ft. Polk, La.	1004	189	18.8
Baltimore AFES	1783	400	22.4
Ft. Jackson, S.C.	443	50	11.3
Total	6804	1398	20.5

*Through June 1966.

meningococcal infection by the various serologic groups and have had to content themselves with measuring the presence or absence of the organism in the nasopharynx of the host population. Table 2 summarizes such a study of meningococcal carrier status in Army inductees since 1964. It indicates that approximately 20 per cent of civilians in the induction age group harbor the organism in their upper respiratory tract at the present time. Of the 20 per cent infected, approximately 6 per cent carry sulfonamide-resistant Group B or C meningococci when entering the service. If we follow the inductee population through the first 16 weeks of basic and advanced individual training, we note that the carrier rate rises to around 35 per cent by the eighth week and in some company-sized units may rise to 75 to 80 per cent between the eighth and sixteenth weeks.[6] When 30 men of one platoon of 44 men were cultured daily for 31 days at Ft. Ord, California, the cumulative total of men with one or more positive cultures for meningococci was 100 per cent. None of these men contracted clinical meningococcal disease during their basic training period. Eight of the 30 (26.6 per cent) harbored sulfadiazine-resistant (0.1 mg. per 100 ml.) meningococci in the upper respiratory tract on one or more days during this study.[31]

Carrier studies in young military-aged adults since 1963 reveal infection rates consistently around 20 per cent. The probable infection rate (healthy carriers) during the first 16 weeks of military training is nearly 100 per cent. Clinical disease is manifest in trainees at the rate of 1.9 per thousand per year; therefore, disease occurs in very few of the recruits infected.[24] Similar data is not available on transmission within other age groups, either military or civilian, since 1960.

SULFONAMIDE RESISTANCE

Feldman[12] considered evidence of the appearance and pattern of sulfonamide resistance and summarized that "it appears . . . as though a slight but definite trend toward greater resistance to sulfadiazine has been taking place since World War II."

Eickhoff and Finland[10] believed it reasonable that resistant strains have always been present in the population in small numbers. In 1964, 64 per cent of strains of meningococci submitted to the Communicable Disease Center were inhibited by 0.1 mg. per 100 ml. of sulfadiazine; only 27 per cent of strains were inhibited at that level during the first six months of 1966. Similarly, in 1964 only 8 per cent of strains required 10.0 mg. per 100 ml. or more of sulfadiazine for inhibition, whereas during the first half of 1966 about 35 per cent of strains were resistant to this concentration of sulfadiazine.[8] The history of the emergence of sulfonamide resistance seems to be one of a few resistant strains of meningococci gradually increasing in prevalence and remaining largely unnoticed until, in the special epidemiologic setting of the military training center, these strains caused enough disease to be studied and brought to general attention in 1963. Almost immediately thereafter Leedom et al.[20] detected sulfonamide-resistant disease in civilians admitted to Los Angeles County General Hospital.

Ivler and others,[18] studying strains from these cases, found 28 per cent of 70 strains resistant to 10 mg. per 100 ml. or more of sulfadiazine. They noted further that addition of *p*-aminobenzoic acid (PABA) reversed sulfadiazine effects on a strain inhibited by 0.1 mg. per 100 ml. of this drug and were the first to report that inoculum size, presence or absence of carbon dioxide, and the culture medium employed influenced the level of sulfadiazine resistance determined in the laboratory. These observations explain more fully the wide differences in reported levels of sulfonamide resistance encountered in different laboratories that are studying the meningococcus. General agreement among investigators on precise culture techniques when determining levels of sulfadiazine resistance should remedy these differences.

MORTALITY

In 1964 and 1965 a total of 654 cases of meningococcic meningitis, with 74 deaths, occurred within United States Army treatment facilities.[24] Of the total number of cases, 196 have known serotypes and were tested for sensitivity to sulfadiazine at the 0.1 mg. per 100 ml. level. An additional 116 case strains were typed but not tested for sulfonamide sensitivity. Table 3 summarizes the results of studies in these cases and the deaths resulting from these cases.[27] Group B meningococci accounted for 85.8 per cent of the cases and 96.8 per cent of the deaths in this study. Group B resistant organisms contributed 54 per cent of

Table 3. *Selected Meningococcal Cases from Deaths Occurring on Army Military Installations, 1964 to 1965**

SEROTYPE	RESISTANT†		SENSITIVE		UNKNOWN		TOTAL	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
A	2	1	6	0	2	0	10	1
B	106	13	66	6	96	11	268	30
C	4	0	10	0	17	0	31	0
NT‡	0	0	2	0	1	0	3	0
Total	112	14	84	6	116	11	312	31

*Includes military and civilian cases with known serotypes in United States and Europe. Source: Special Telegraphic Report of Selected Diseases (RCS MED-16).

†0.1 mg./100 ml.

‡Nontypable.

cases and caused 65 per cent of deaths in the group tested for sensitivity. The case fatality rate was 11.3 per cent. This rate occurred in the most favorable age group from the recovery standpoint. Higher rates, such as in California for 1962 and 1963 (19.1 per cent), reflect the higher mortality associated with disease in infants and in adults over 40 years of age.

Overwhelming meningococcemia, with or without meningitis, and characterized by gross purpuric lesions and vasomotor collapse, is relatively infrequent, occurring in less than 10 per cent of cases. Mortality of this type of case ranges from 33 to 50 per cent in spite of therapy.[1] The interval between onset of illness and death has been as short as five hours in military cases reported at Ft. Ord.[3]

PROPHYLAXIS

Dingle and Finland[9] observed that "control and prevention of an infectious disease are dependent primarily on knowledge of the epidemiology and immunology of that infection. Cerebrospinal fever has presented a puzzling problem in these respects because case to case spread has been proved only rarely and an understanding of the role of immunity has been hindered by many technical difficulties." Determining the immunologic status of threatened populations remains the foremost barrier in finding effective and rational control measures.

In the absence of detailed information on the immune status of individuals, the philosophy of "treating" the entire population at risk evolved after Fairbrother[11] concluded that the carrier state could be altered by the use of sulfonamide derivatives. Intensive studies on carrier rates, carrier relationships to disease, and the effect of chemotherapy with the sulfonamides were conducted in the early 1940's.[4, 9, 19, 26, 29] Kuhns et al.[19] wrote that "the effectiveness of the prophylaxis . . . depended on (1) treating all individuals in the group simultaneously, (2) treating all personnel who joined the group subsequent to the institution of prophylaxis before they were incorporated into the group and (3) keeping the treated group closed to reinfection from outside sources." These basic tenets are as true today as they were in 1943 and remain the guidance, if not the practice, in all chemoprophylactic programs and studies in the evaluation of prophylactic agents. Kuhns' comments describe the basic epidemiologic philosophy behind prophylaxis; that is, treat the entire population within which transmission of meningococci is nearly 100 per cent,[26, 29, 31] and then isolate this population so that further introduction of meningococci cannot occur. In effect, this is an eradication procedure. Contrast this with the prevalent practice of administering prophylactic drugs to close contacts of cases who then freely circulate in the same infected population in which they acquired their original infection. The latter practice assumes more absurdity (except for pure psychologic reasons) when sulfadiazine is administered at a time sulfonamide-resistant meningococci are present in a significant proportion of the infected population.

Millar et al.[25] and later Gauld et al.[15] described meningococcal outbreaks at the San Diego Naval Training Center and at Fort Ord, California, that occurred in spite of repeated chemoprophylactic programs. The investigations revealed sulfonamide-resistant organisms in a high

Table 4. *Meningococcal Cases in Basic Trainees in the First Eight Weeks of Training at Ft. Leonard Wood, November 1, 1965 to August 1, 1966**

	FIRST THROUGH FOURTH TRAINING WEEK	FIFTH THROUGH EIGHTH TRAINING WEEK
Bicillin	17	18
No Bicillin	5	9

*Trainees at Fort Leonard Wood given benzathine penicillin (Bicillin) 1.2 million units on the third day after arrival at the reception center (a few later but none later than seven days). Bicillin administered November 1 to April 1 as a streptococcal prophylaxis.

percentage of cases and in the carrier population. Chemoprophylactic measures had apparently selected out the resistant strains of meningococci, which existed in a high enough proportion to spread throughout the recruit populations. The reason for the failure of sulfonamide prophylaxis was clear and guidance on the use of sulfonamides for chemoprophylaxis was changed by The Surgeon General of the Army in 1964 to reflect this altered situation. This guidance provides that sulfonamides will not be used chemoprophylactically unless carrier studies reveal that less than 10 per cent of the infected population are harboring sulfonamide-resistant meningococci. This marked the end of 20 years of reliance on sulfonamide prophylaxis to control epidemics of meningococcal disease in the military.

The effect of antibiotics and various sulfonamide potentiators in combination with the sulfonamides on the meningococcal carrier state is not well known. Limited studies have been reported, none of which have been carried out on a large group suitably isolated to forestall reinfection from the surrounding population. Millar et al.[25] gave oral penicillin G, one million units in two divided doses daily for four days, to one company. Daily cultures showed a carrier reduction from 56 per cent positive nasopharyngeal cultures to 5 per cent initially then a rise to 53 per cent at the end of 10 days. In one study attempt at Fort Ord, 1.2 million units of phenoxypenicillin was administered four times daily for four days (total 19.2 million units) to 80 men. Although the carrier rate was reduced to zero on the second day following penicillin administration, the study was abandoned because the group was not isolated after the second day post treatment. The significant finding in this study is that 50 per cent of the men experienced severe diarrhea.[16] This complication effectively nullified oral penicillin use at this dosage in mass prophylaxis.

Feldman[12] reports that "numerous prophylaxis trials have been attempted within the past year and a half with various antibiotics, including the penicillins and tetracycline. These have been used in rather massive doses for 10 days or more. While they appear to have a knockdown effect on the carrier rates, the preprogram carrier rate very quickly re-establishes itself as soon as the antibiotics are removed." No further information on the conduct of these studies is given.

Trainees at Fort Leonard Wood are given 1.2 million units of benzathine penicillin (Bicillin) on the third day after arrival at the reception center as a prophylaxis against streptococcal disease and rheumatic fever. Penicillin in this dosage has not reduced the occurrence of meningococcal disease in this large group of trainees (Table 4).[28]

Similarly disappointing results, as with the antibiotics, have occurred at Fort Ord in 1964, when nalidixic acid, and in 1966 at Fort

Knox and Fort Dix, when trimethoprim, were used as sulfonamide potentiators in limited carrier control studies. These chemicals as well as pyrimethamine[2] have been shown to be highly effective in stopping growth of sulfonamide-resistant meningococci in vitro.[33]

In summary, sulfadiazine is no longer a reliable mass chemoprophylactic agent for the control of meningococcal disease when sulfonamide-resistant organisms are present in a significant portion of the carrier population. The antibiotics and sulfonamides with sulfonamide-potentiating chemicals, in limited studies, show little promise in the mass prophylactic vacuum for meningococcal disease control.

TREATMENT

Eickhoff and Finland[10] and Ivler et al.[18] have independently reported that approximately 30 per cent of meningococcal strains submitted to them from civilian cases are resistant to 10 mg. per 100 ml. or more of sulfadiazine. Fortunately for the clinician, no resistance has been demonstrated to penicillin, and Lepper et al.[21] have shown that penicillin G in high doses is at least as effective as sulfisoxazole in the treatment of meningitis. More recently Levin and Painter[22] have reported a series of 28 patients treated with penicillin G with a mortality of 3.6 per cent. Therefore, if there is no known allergy to penicillin, this antibiotic should be used as soon as a patient is suspected of having meningococcal infection.

Speed in diagnosis and beginning therapy is the keystone of a favorable prognosis; consequently, after blood and spinal fluid have been obtained for later cultures, an initial loading dose of one million units of aqueous penicillin diluted in 30 to 50 cc. of fluid should be administered intravenously over a 10 minute period. This same dose of penicillin is given hourly until the patient's clinical course has favorably stabilized and he has been afebrile for at least 48 hours. Thus, 24 million units of penicillin is given each 24 hours. Thereafter, intramuscular procaine penicillin in a dose of 600,000 units every six to eight hours is given to complete a ten-day course of therapy. For patients known to be allergic to penicillin, chloramphenicol 4.0 gm., tetracycline 2.0 gm., or erythromycin 2.0 gm. should be given intravenously each 24 hours in divided doses. The maximum allowable intravenous dose is administered initially. Oral administration of these drugs may be used when the patient has been afebrile for 48 hours to complete a ten-day course. Dosages should be reduced proportionately by weight for children.

Early evaluation of fluid and electrolyte balance is important. Some patients with meningococcal meningitis excrete an increased amount of urine on the second and third days of illness. Mild hypokalemia is relatively frequent. Rarely, altered antidiuretic hormone secretion seems to occur leading ultimately to the signs and symptoms of water intoxication. This should be suspected in the presence of a normal blood urea nitrogen, good renal function, low serum sodium, high urine specific gravity, and sodium excretion. It responds to fluid restriction. Occasionally, mannitol diuresis or hypertonic saline infusions are necessary.

In the severely ill patient, central venous pressure should be monitored. If shock has occurred, it must be rapidly corrected. Administration of intravenous isotonic saline fluids is governed by the urinary output and the central venous pressure. Intermittent intravenous mannitol to maintain the urinary output at 60 cc. per hour is useful. Although the role of vasopressor agents, corticosteroids, and vasodilator agents in septicemic shock syndromes is controversial, most clinicians employ them in this disease.[32] Initially, a vasopressor, such as metaraminol, may be used to maintain systolic blood pressure in the 80 to 90 mm. range and assure adequate cerebral and coronary circulation. If shock persists, 1000 mg. of hydrocortisone can be given intravenously, followed by 500 mg. every six hours for 48 hours. Intravenous infusion of isoproterenol, 0.2 mg. per 100 ml. administered at the rate of 0.5 to 3 ml. per min. has been effective in reversing unresponsive shock.[22] Prior expansion of the intravascular volume by intravenous fluids, specifically sodium bicarbonate (45 to 180 mEq. per hr.), is also recommended in refractory hypotension. In response, an adequately expanded blood volume is best indicated by a central venous pressure of 12 cm. of water above the estimated right atrial level. Finally, isoproterenol hydrochloride, 1 mg. per 500 cc. in normal saline given at 0.1 to 0.2 mg. per hour, has an inotropic effect on the heart and, as a beta adrenergic stimulator, will cause peripheral vasodilatation. This will decrease visceral vasoconstriction and, it is hoped, interrupt the ischemic anoxia and pooling of blood. The net result is a rise in blood pressure and, more important, increased blood flow through capillary beds of vital organs. When this agent is used, the patient must be observed carefully for the development of arrhythmias or tachycardia. Its use should be discontinued if either occurs.

Evidence of myocardial insufficiency is indicated by a rising central venous pressure, ventricular gallop, or basilar rales. Digitalization by intravenous infusion of a rapidly acting digitalis preparation (lanatoside-C) is indicated.

Rapidly advancing intracranial pressure with rising hypertension, papilledema, and vomiting may occasionally demand the use of intravenous urea or mannitol and adrenal steroids.

Most patients recover rapidly, but ambulation and activity should be restricted during the initial 10 days of therapy. This may obviate the unexpected death from myocarditis and arrhythmia. Progressive ambulation is then permitted over the next three to four weeks of convalescence.

SUMMARY

There has been a rise in the occurrence of meningococcal disease in the United States and a concurrent rise in military cases during the past three years. This rise is occurring according to the pattern that has been observed in the United States registration area since 1900 and corresponds to an 8 to 11 year cycle. One significant difference exists between the present rise in cases and increases in prior decades; this rise is characterized by the majority of cases being caused by the Group B meningococcus whereas prior outbreaks were caused primarily by the Group A organism. Within the total framework of the increase in meningococcal disease, due mainly to the sulfonamide-resistant Group B meningococci, localized epidemics have occurred in which sulfonamide-resistant meningococci have played a significant role. The importance of sulfonamide resistance in meningococcal disease and its treatment and prophylaxis are discussed.

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Malaria: The Changing Outlook

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There is still some uncertainty as to the origin of malaria in the Americas. A few authors have contended that the disease existed in the hemisphere before the arrival of the early explorers, colonizers, and traders. It is certain, however, that the Spanish, French, and British colonizers and the large numbers of slaves imported from Africa repeatedly introduced malaria parasites into the Americas. Malaria was recorded in eastern Massachusetts in 1634,[6] and it became the number one public health problem of the southeastern United States, and of much of the lower Mississippi River Basin, during the nineteenth and early part of the twentieth century. It frequently occurred in localized epidemics in the northeastern United States and occasionally in southern Ontario.

Efforts to control the disease in the United States began in a few areas in the 1920's, were intensified during the 1930's, and under the impetus of World War II were expanded substantially, with much success in populated areas. The experience gained during the war permitted development of effective synthetic antimalarials and taught us how to utilize the residual effect of DDT and other chlorinated hydrocarbon insecticides. These advances led to the initiation of our National Malaria Eradication Program on July 1, 1947.

The successful eradication of malaria from the United States, from most of Venezuela, from large areas of British Guiana, and from limited areas of other parts of the world led to the decision by the Pan American Health Organization at its Pan American Sanitary Conference in Santiago, Chile, in 1954, to promote the intensification and coordination of antimalaria work with the view of achieving malaria eradication in the Western Hemisphere. The next year the World Health Organization, at the World Health Assembly in Mexico, voted to give priority attention to global eradication of malaria. The United Nations Children's Fund agreed to support it financially. In 1957 the Congress of the United States took a historic step when it declared that it was the policy of the United States to assist other peoples in their efforts to eradicate malaria from the world.

Pampana and Russell in 1955 estimated that more than a quarter of a billion persons throughout the world have clinical attacks of malaria annually and that at least 2.5 million die each year from this disease.

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Eradication was undertaken following the demonstration that semiannual spraying, with a formulation of 75 per cent water-dispersible DDT, of the interior walls and ceilings of human habitations and of under surfaces of larger pieces of furniture, in such a manner as to leave a residual film of 1 to 2 gm. of the insecticide per square meter of sprayed surface, kills the potentially infected Anopheles mosquitoes alighting on the treated surface and prevents transmission of malaria. Relapses of falciparum malaria rarely occur after one year, and of vivax malaria, after two to two and one-half years; therefore, if all human carriers of the malaria parasite can be located and effectively treated, then a campaign of malaria eradication can be expected to be successful. A rather simple technique for the location of the parasite carriers has evolved on the assumption that the human carrier who is infective for the anopheline mosquitoes will have fever or chills or both during his attack or relapse. The case finding program is designated as *surveillance*. The surveillance workers visit each habitation in the eradication area at least monthly (fortnightly in India and certain other countries) and ask on each visit if anyone in the household presently has fever or chills or has had these symptoms since the last visit. Also, he questions whether any visitors from outside the area have been sick or whether there is any illness in the household. If fever or other suspicious symptoms are elicited, chloroquine suppressive treatment is administered on the spot and a blood smear is taken from the fever victim. If subsequently this smear is found to be positive, radical treatment for malaria (primaquine) is administered to the patient daily for the full course.

CURRENT STATUS OF WORLD ERADICATION OF MALARIA

As of December 31, 1965, according to the World Health Organization, 1214 million people, or 77 per cent of the estimated population in the originally malarious areas of the world, live in areas where malaria has been eradicated or where eradication programs are in progress.[7] The population of areas in the maintenance and consolidation phases—and thus freed from the risk of endemic malaria—now amounts to 905 million (over 57 per cent of the population of the originally malarious areas). An additional 265 million people live in areas that are in the attack phase of the eradication campaign, and 43 million in areas in the preparatory phase. Unfortunately, more than 362 million live in areas where eradication programs have not yet started. More than half of these are in Africa.

An idea of the magnitude of malaria eradication undertakings can be gained from the expenditures for the period of 1958 to 1962, $571.9 million, and the estimation that $1,342.5 million (in terms of the 1960 dollar) would be required to complete the program.[2] In India, as early as 1960, more than 100,000 workers were employed in the spraying program and 50,000 surveillance agents were in the process of mobilization and training. Administrative and financing problems, therefore, have been enormous. Johnson[3] indicates a total expenditure of more than $242 million, from national and international sources, in India between 1958 and 1964, and of almost $20 million during 1965.

MAJOR PROBLEMS ASSOCIATED WITH ACHIEVEMENT OF MALARIA ERADICATION

Two major technologic difficulties in the eradication program have arisen, namely, the development of anopheline resistance to the insecticide utilized, and human tolerance to the therapeutic or chemoprophylactic agent. The Eleventh Report of the WHO Expert Committee on Malaria (1965) indicates that one vector species of Anopheles is resistant to DDT only, ten species are resistant to dieldrin only, and 11 are resistant to both DDT and dieldrin. Fortunately, there has been little change in these numbers since 1961. It is only in limited areas of the world that the development of resistance to the commonly used insecticides, DDT and dieldrin, has been a serious threat to the eradication campaign. Certain localities in El Salvador, Guatemala, Honduras, and Nicaragua have proved very difficult.

Resistance to the various antimalarial drugs probably has been in existence for decades or longer. Experimentally, resistance to proguanil and chloroguanide was demonstrated in 1947, and soon afterward resistance to pyrimethamine (Daraprim) reduced its use as a suppressive drug. The embarking of many nations on a campaign of global malaria eradication among a population of more than a billion people, the routine administration of at least one dose of a suppressive drug to everyone reporting fever, and the initiation of an active program to provide full treatment to every parasite-positive person has resulted in the unparalleled administration of a few antimalarial drugs to millions of people indigenous to malaria areas. Selected groups of military personnel, industrial population, travelers, and others have been maintained on chemoprophylaxis for long periods of time. Resistance to the drug chloroquine, most extensively used as a suppressive and as a chemotherapeutic in malaria infections, was not demonstrated until 1961, when Moore and Lanier[5] isolated a strain of Plasmodium falciparum from two patients from Colombia, South America, who failed to respond to chloroquine therapy. Since then similar isolations have been made in Thailand, Malaya, Cambodia, Vietnam, Brazil, British Guiana, and Venezuela. Strains of P. falciparum resistant to proguanil, mepacrine, and pyrimethamine, in addition to chloroquine, have been found. Early studies indicated susceptibility to quinine, but more extensive experience in the treatment of P. falciparum-resistant strains among American troops in Vietnam or returnees from Vietnam have indicated that only about 60 per cent may be successfully treated with quinine. Malaria became recognized as a major health problem among our troops in Vietnam when 1801 contracted the disease in 1965 and a total of 63,035 man days were lost from duty. Early in 1966 it was reported that malaria accounted for evacuation of as many United States troops from the Vietnam theater as war wounds.

The Walter Reed Army Institute of Research, collaborating with civilian medical institutions (including the University of Chicago), has carried out extensive drug testing programs, which have demonstrated the utility of diaminodiphenylsulfone (DDS), the widely used antileprosy drug, as a chemoprophylactic and chemotherapeutic agent against malaria. In addition to the prophylactic administration of the standard pill containing 300 mg. of chloroquine phosphate (base) and 25 mg. of primaquine once per week, servicemen in Vietnam are given one 25 mg. DDS pill every day; this is continued for one month after they leave Vietnam. The addition of DDS in the prevention and treatment of malaria is estimated to reduce by one-half the number of soldiers stricken with malaria. It is believed that those who are stricken will be able to return to duty in two or three weeks, instead of six to eight weeks as formerly, and that the chances of a relapse will be cut from

40 per cent to 4 per cent (Department of Defense Release, July 6, 1966). Military sources report that P. vivax malaria in Vietnam is controlled with chloroquine-primaquine drugs. It is quite probable that massive suppressive use of DDS will eventually lead to development of strains of P. falciparum resistant to it, but meanwhile this drug represents a critical breakthrough and search continues for alternative drug measures.

RECENT UNITED STATES EXPERIENCE WITH MALARIA

Each year nearly two million United States civilians travel overseas (exclusive of Mexico and Canada) and a substantial number of them visit or live in malarious areas. Tourism, commercial interests, political activities (State Department, cultural affairs, Peace Corps volunteers), religious concerns, and a variety of other motives lead to the exposure of many individuals apart from any military operations.

Military campaigns in tropical areas have been notoriously vulnerable to the depredations of malaria. Within our own country, the campaigns in 1860 to 1865 were seriously impeded by the disease. In World Wars I and II and the Korean incident malaria was an implacable foe. Currently in Vietnam, the deployment of nonimmune troops in highly malarious areas has been possible only by rigid administration of antimalarial prophylaxis.

The June 4, 1966, Morbidity and Mortality Weekly Reports provided a summary of the total number of cases of malaria (military and civilian) with onset of illness in the United States and Puerto Rico by years for the past 10 years as follows: 1956, 125; 1957, 103; 1958, 72; 1959, 54; 1960, 63; 1961, 85; 1962, 119; 1963, 148; 1964, 171; and 1965, 156.

The Communicable Disease Center reported a total of 156 cases of malaria occurring in the United States in 1965. Of the 144 cases in which specific identification was known, 87 were caused by Plasmodium vivax, 39 by P. falciparum, 13 by P. malariae, and 5 by P. ovale. Civilians accounted for 105 cases (17 were Peace Corps workers, 15 were seamen, and 5 were among missionary families) and 51 cases were in military personnel, 36 of which originated in South Vietnam. The country of origin could be defined in 113 cases; 66 patients were infected in Asia, 51 in Africa, eight in Central America and the Caribbean, eight in South America, and the remainder from scattered areas. Thirty-five military personnel contracted malaria in South Vietnam and subsequently had an onset of illness in the United States or Puerto Rico in 1965. P. falciparum was the etiologic agent in 20 cases, and P. vivax in 12; the species was not identified in three cases. Nine servicemen who had acquired falciparum malaria in South Vietnam just before or shortly after their discharge from service had an initial onset of illness in the United States; there were two fatalities among them. Recently a civilian returnee from North Africa died of malaria in Alexandria, Virginia.

The Parasitic Disease Unit of the Communicable Disease Center also received epidemiologic data during 1965 on 480 cases of malaria in military personnel who had an onset of illness in South Vietnam and were transferred to hospitals in the United States for additional treatment. It is believed that more than 80 per cent of these were chloroquine-resistant falciparum cases. Since these soldiers were on antimalarial chemotherapy and under medical supervision when they entered the United States, it was thought that they posed a lesser threat of introducing malaria into the United States.

According to Dr. Robert L. Kaiser, Chief of Parasitic Diseases Section, Epidemiology Branch of the Communicable Disease Center, 149 cases of imported malaria with onset in the United States occurred in the first six months of 1966. In addition, two cryptic cases of malaria occurred in Kentucky. Of these 151 cases, 100 were in military personnel and 51 in civilians. The parasite species was identified in 132 of the 151 cases as follows: P. vivax, 76; P. falciparum, 44; P. ovale, 4; P. malariae, 1; mixed infections, 7. P. vivax accounted for 57.6 per cent of all cases and for 33 per cent in the military, whereas P. falciparum was responsible for 38 per cent of the military cases and 24 per cent of the civilian cases.

Distribution by area of acquisition of 149 cases of malaria in the United States from January to June, 1966, indicated that 29 of the 49 civilian cases were acquired in Africa and 11 in Asia, whereas 97 of the 100 cases among the military were acquired in Asia.

OPPORTUNITY FOR REINTRODUCTION OF MALARIA TRANSMISSION IN THE UNITED STATES

Associated with the Korean incident there were between 25,000 and 28,000 troops who returned to the United States with either primary attacks or relapses of malaria. A total of 85 secondary cases were demonstrated to be traceable to these returning servicemen, including an epidemic of 35 cases among a group of Camp Fire Girls at Lake Vera, Nevada County, California.[1]

The Morbidity and Mortality Weekly Reports of August 21, 1965, document the first transmission of malaria in the United States since 1957 as occurring on July 10, 1964, in an Army wife at Ft. Benning, Georgia, due to P. vivax. Presumably transmission occurred from an infected soldier, returned from Korea, whose case was not diagnosed until after he left Ft. Benning, but who was ill during the period June 3 to 23, 1964, and in whose blood vivax parasites were subsequently demonstrated. Anopheles quadrimaculatus were found in the same residential area. The following year, on May 22, 1965, another Army wife was confirmed as having Plasmodium vivax parasites and investigation revealed that she had been living in the same residential area in July, 1964. It is presumed that this was an instance of prolonged incubation period.

The May 28, 1966, Morbidity and Mortality Reports state that on May 2, 1966, the five year old daughter of a noncommissioned officer stationed at Ft. Knox, Kentucky, developed malaria (vivax), and her three and a half year old brother also was demonstrated to have parasites. Both children were born at Ireland Army Hospital, Ft. Knox, Kentucky, and neither child had ever traveled outside of Kentucky or had a history of blood transfusions. These two cases were presumed to be delayed primary cases of vivax malaria whose transmission occurred during the summer of 1965 from an unknown serviceman-carrier of this species of malaria.

Public health personnel are encouraged by the fact that documented evidence of transmission exists in only two instances of more than 100 cases of malaria annually with onset of the illness in the United States and Puerto Rico from 1956 through 1965; nevertheless this does indicate the necessity to be on the outlook for transmission. Both the cited episodes were infections with P. vivax, which has the longer period of relapses and the wider adaptation to temperature range within the United States.

The real threat of malaria to our citizenry from travel, service, or residence in malarious areas must be recognized. The emergence of resistant strains of P. falciparum in various countries threatens even those on suppressive therapy. Military personnel are protected by a much greater efficiency in maintenance of good chemoprophylactic regimen, diagnosis, and prompt therapy than nonmilitary travelers. Stateside physicians must be alerted to the possibility of malaria in both released veterans and civilians returning from malarious areas. Returnees from regions where resistant strains of P. falciparum are known to occur must be handled with extreme caution since malaria deaths have occurred within our boundaries, both in civilian and veteran population, during the past year. Health departments must be vigilant regarding the possibility of transmission by the indigenous vectors when imported cases of malaria occur.

Since the United States does not seem destined to develop an isolationist attitude and to keep its citizenry within national boundaries, it appears that we shall have to face up to a major choice of helping eradicate malaria on a global basis or of being forever alert to the early diagnosis of malaria in citizens returning, or visitors entering, from malarious areas.

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The Rise in Venereal Disease: Epidemiology and Prevention

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"Studies of 1000 male gonorrhea patients, aged 15 to 60 years, and representing the lower social and economic group of a section of Los Angeles, revealed that 80 per cent had a history of previous venereal infection and 54 per cent had acquired their initial infection between the ages of 15 and 19 years. Further, 26 per cent of those reporting with a first infection returned with a new infection during the six months' duration of the study."[18]

This paragraph from *WHO Chronicle* sets a discussion of genitoinfectious diseases apart from the remainder of this program. The spread and the control of these diseases are highly personal matters. Control cannot be attained by sanitation, draining swamps, or eliminating animal reservoirs of infection. Control of the genitoinfectious diseases is possible only by a patient's cooperation in breaking the chain of infection and by treatment. The introductory paragraph emphasizes that promiscuity will be with us so long as the sex drive remains an almost uncontrollable biologic urge. We know that age and previous episodes of infection are not deterrents to new exposures.

In consideration of the spread and control of genitoinfectious or venereal diseases it is necessary from a practical viewpoint to consider only syphilis and gonorrhea. Chancroid and lymphopathia venereum have become quite uncommon. Though trichomoniasis, Reiter's disease, and possibly even herpes genitalis and granuloma inguinale might by definition be included in the genitoinfectious diseases, their consideration would carry us too far afield. I will focus my attention upon syphilis primarily, with only a few comments concerning gonorrhea, even though it is several times more prevalent than syphilis.

Syphilis is chosen over gonorrhea for a discussion of spread and control for several reasons. It is a major disease accompanied by high morbidity and a not inconsiderable mortality if untreated. Because of its effect upon health and production of disability, its cost to society is great. The incubation period is of such length that epidemiologic investigation and treatment are possible and can be successful, with few exceptions. Diagnosis is relatively simple and definitive. By contrast, gonorrhea, though it has a much greater prevalence, is acknowledged to be practically uncontrollable through epidemiologic methods. The sexually promiscuous may be infected repeatedly; the diagnosis is difficult to establish, particularly in the female carrier, and life-threatening complications rarely develop. Even with the haphazard symptomatic and clinical treatment taken by patients today, the incidence of complications which may cause sterility in either sex has been greatly reduced, although the development of treatment-resistant strains of the gonococcus may alter this. In addition, the incubation period is so short that case finding for prophylactic treatment is almost impossible. Thus, syphilis offers the prototype for epidemiologic control in the area of the genitoinfectious diseases.

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BIOLOGIC ASPECTS OF SYPHILIS

A brief review of the biologic course of untreated syphilis is essential for orientation to the problems of epidemiology and an understand- of the morbidity and mortality which may result from lack of treatment.

The infectious agent, Treponema pallidum, is an anaerobe quite readily obtained from a superficial lesion (the chancre, condyloma, or mucous patch), and less easily from a scarified macule or papule of the skin or by puncture of a lymph node. The active T. pallidum in a satisfactory darkfield preparation shows a characteristic motility which, along with its shape, makes its differentiation from other spirochetes quite easy in the eyes of an experienced microscopist. This extremely delicate organism usually is killed by anything which alters surface tension, such as a soapy solution or even minor changes from isotonicity of saline solutions, and by exposure to air and drying. On the other hand, it may remain viable in serum for many hours and it may be "quick frozen" and be viable on thawing.

The characteristics of T. pallidum, then, point to its obligatory transmission from one moist area to another with probably an almost *immediate* necessity of entry to deeper tissues through a break in either the skin or mucous membrane. Because of these limitations, transmission by a vector other than the human occurs rarely, though transmission is possible, as shown in our clinic, by a razor, a douche tip, the mouth of a whiskey bottle, or by chewing gum or premasticated food initially contaminated by one in the infectious stage of disease. It seems probable that the unbroken skin cannot be penetrated by T. pallidum; mild abrasion, as in the shaved rabbit skin, permits penetration. Maceration of the skin may break the cutaneous barrier, as shown by a chancre on a grandmother's wrist following sucking by an infant with infectious prenatal syphilis. Chancre of the finger in the dentist and physician is not unknown.

On the other hand, we have encountered (in prepenicillin days) massive contamination of the face, nostrils, and lips in a laboratory accident without infection of the victim. In our clinic, the epidemiologic experience with first infections in persons promiscuous for years, and with infection in marital partners, one of whom had infectious lesions, points certainly to a barrier to the entry of T. pallidum through the unbroken skin and possibly through the unbroken mucous membrane. (Of 96 marital partners 18 escaped infection even though their spouses had infectious lesions.[20])

Statistics from several clinics have shown in the past that T. pal-

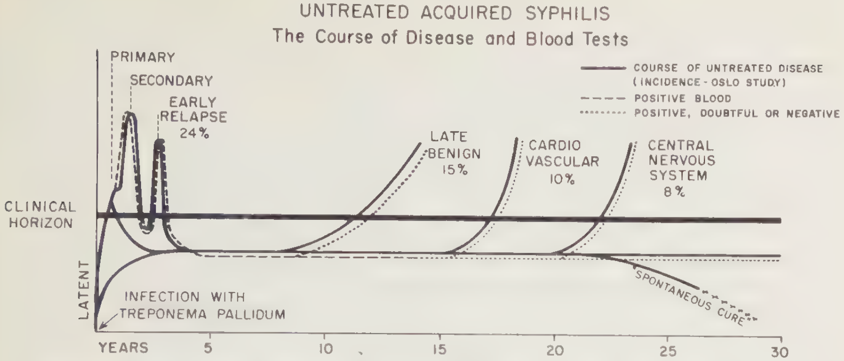

Figure 1. The natural history of untreated acquired syphilis. (Modified from original by Dr. Hugh J. Morgan, courtesy South. M. J. 26:18, 1933. Incidence of clinical disease from Clark and Danbolt,[4] J. Chron. Dis. 2:311, 1955.)

lidum gains entry in the genital area in heterosexual exposure in 95 per cent of instances, in round figures, with the remaining 5 per cent representing an oral portal of entry from kissing or other intimacies. (Comparable data are not available from homosexual experiences.) All other routes of infection represent such a minuscule percentage of infection that public health personnel need give little attention to them.

However, the private practitioner must recognize the possibility of extragenital portals of entry by keeping syphilis in mind in history taking, especially when faced with serologic evidence of syphilis or an extragenital ulcer. Tobias[32] appropriately quotes Fournier, the great syphilographer of the last century: "To diagnose an extragenital chancre is simple, to keep it in mind is difficult." I doubt, too, in such history taking that anyone other than a physician should explore the patient's sex play, or would have the scientific knowledge to establish possible spread of syphilis by infectious lesions of prenatal syphilis.

A quick review of the natural history of untreated syphilis can be provided best by a graph as in Figure 1. The primary lesion or chancre may appear some 10 to 20 days after exposure. In males the portal of entry is commonly recognized, but an intravaginal or cervical chancre will certainly not be noted and even a vulval chancre may not be identified, nor the rectal lesion of the homosexual. The chancre heals spontaneously in two to four weeks, to be followed usually by some manifestation of widespread spirochetemia, commonly revealed by systemic symptoms of infection, characteristic rashes of skin and mucosa, condylomas, alopecia, lymphadenopathy, and very rarely hepatitis or skeletal disease.

Infectious relapse is not infrequent, particularly within the first four years following infection. This characteristically does not show itself with a generalized eruption as in the initial secondary stage, there being a paucity of skin lesions. Thus the frequent mucous patches and other moist lesions, usually asymptomatic, are of particular importance in spread since the "red flag" of a rash is missing. Review of Boeck's Oslo material, in 1955, by Clark and Danbolt[4] showed that early relapse occurred in 24 per cent of untreated patients. (Among inadequately treated patients the relapse rate is higher, which has its implications for persons with early syphilis who receive *antibiotics for intercurrent disease but in inadequate amounts to cure syphilis.*[13]) Within the first four years of infection "tissue immunity" is not firmly established, permitting relapse lesions probably as a result of recurrent spirochetemia. An example is the incidence of miscarriage, stillbirth, and birth of a syphilitic child in *untreated* mothers, which is highest in the first year or two of the infection and decreases in subsequent years to become rare after four or five years. Realistically, then, epidemiologic investigation after the second year of the infection is unrewarding, not only because of rarity of infectious relapse[4, 17] but because an extended lapse of time following exposure makes it almost impossible to trace contacts in a promiscuous and transient population. Therefore field workers in public health limit their epidemiologic activities to the first year of the patient's infection.

However, the practitioner of medicine with responsibility to the individual should not lose sight of the *possibility of relapse and infectiousness in early latency to roughly four years.* This is particularly true in marriage and the *major excuse* for premarital blood testing. Seventy-five years ago, before T. pallidum had been discovered, and before blood tests and arsenotherapy were known, Fournier, by clinical observation set the conditions under which the syphilitic person had the "moral right to marry." He said, "If not always, at least in an enormous majority of cases, the husbands that communicate syphilis to their wives are those who have entered into marriage with a *syphilis still young*—that is to say, with a syphilis dating back several months, one year, two years, rarely three and four years." Those interested in syphilis have seen Fournier's clinical observations substantiated time and again in marriage.[20]

My discussion, then, does not extend beyond the early years of the disease, since syphilis thereafter is rarely significant from the point of view of public health and spread of disease. After these early years, syphilis is of interest to the person harboring the treponeme and the resulting clinical disease and disability. To be sure, the socioeconomic costs of cardiovascular syphilis and syphilis of the central nervous system, particularly, do have interest for the tax-paying body politic.

EPIDEMIOLOGIC CONTROL

Returning then to the epidemiology of syphilis, case finding and control would seem to be simple. There is nothing mysterious about the spread of syphilis (or of the other genitoinfectious diseases for that matter). To put it simply, the path of the fragile, delicate, infectious agent, which must be transmitted for practical purposes from person to person by intimate contact, should be identified easily and the chain of spread be broken readily.

However, the facts are to the contrary. As was said earlier, syphilis accompanies a biologic instinct which commonly will not be gainsaid. These special circumstances place genitoinfectious diseases in an entirely different category epidemiologically from all other infectious diseases, many of which do not lend themselves so apparently to easy control and prevention. The epidemiology of syphilis is a highly personal matter, accentuated commonly by the clandestine aspects of exposure to the disease. The hurdle, then, of applying a simple epidemiologic system lies in the psychologic and emotional aspects of the very intimate personal relationships involved. Contact investigation commonly requires the admission of promiscuity, broken marriage vows, and a breaking of morals, the extent depending upon the home environment in which the person was reared. Thus, guilt, anxiety, the fear of marital strife and even separation, and, for the homosexual, the attitudes of society toward such practices and the anticipation of punitive legal, social, and economic sanctions, complicate case finding and tie the hands of epidemiologists in a manner not met in any other infectious disease.

It is generally accepted that an average of four or five contacts will be named for each person known to have infectious syphilis. The control of disease depends upon finding these contacts and upon their examination and treatment. The finding of contacts requires interest in and knowledge of how to approach the infected person, so that he may understand the need for divulging the names of those with whom he has had intimate relationships. That the epidemiologic control of syphilis is relatively easy and highly successful was demonstrated first by Munson[22] in 1932 and then by Nelson[23] in Massachusetts and by Smith and Brumfield[28] in Virginia. E. Gurney Clark[5] and others in the Vanderbilt University Hospital Clinic extended the demonstration of the practicality of contact investigation and case finding in the control of syphilis. If the public health clinic or the university hospital is the place in which the diagnosis is made and the treatment given, epidemiologic methods can be quite easily employed. The clinic physician, the social worker, and the public health nurse are attuned to establish the rapport with patients so essential to obtaining the names of contacts and thereby attaining the epidemiologic objectives.

We must be realistic, however, and observe that the average clinic patient is not equally plagued by the same restrictions and anxieties as at least some of the patients consulting a private physician. The social status and the educational level of many clinic patients is such that there is less remorse or self-condemnation for promiscuity or marital unfaithfulness. Anyone who has had an active role in venereal disease clinics recognizes that a certain segment of the clinic population is unmoral or even amoral. Among these, promiscuity may be a way of life and the naming of heterosexual contacts is often without concern. As one moves upward in the social and educational strata one encounters more and more concern expressed as anxiety and guilt, and a single misadventure of a married woman of a highly moral family background may represent the epitome of psychic trauma.

That the application of epidemiologic control to syphilis met with success appears as a succinct summary in the report of the Task Force[9] of 1962. The dynamic leadership of Dr. Thomas Parran, Surgeon General of the U.S. Public Health Service, in the years following 1936, resulted in "the period of building the control apparatus" (1941 to 1947). During this time the number of reported cases of infectious syphilis rose from 68,000 to 106,000 annually, and the rate per 100,000 population rose from 52 to 76. In the second period, 1948 to 1953, labeled a "period of 'orderly decline,'" there followed a decrease of both cases reported and case rate per 100,000. The least profitable efforts in control were reduced and the Rapid Treatment Centers were closed during this period. During the third period, 1954 to 1957, the number of reported cases and the rate per 100,000 reached the lowest point, a period of response "to the forces of disintegration inherent in this dramatic success" (Fig. 2).

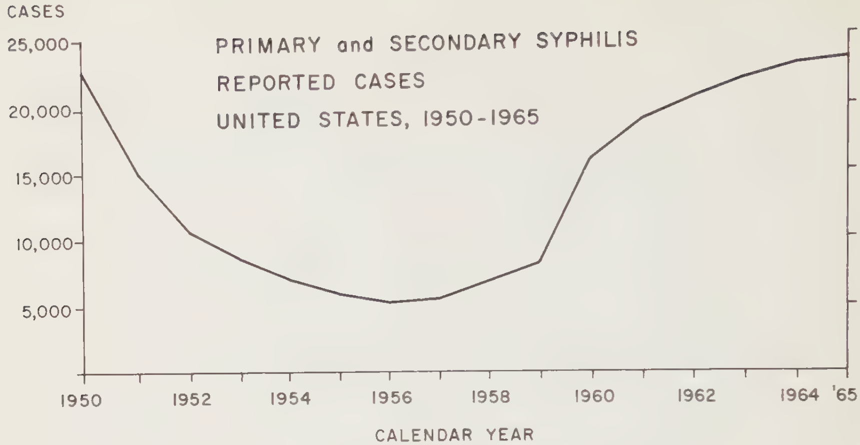

Figure 2. (Brown,[3] courtesy South. M. J. 59:640, 1966.)

As a result those in the health field were lulled into a false belief that the problem of syphilis had been solved. Federal appropriations for venereal disease control dropped from 9.8 to 3 million dollars in a period of two years, state support remaining at about its former level. The loss of federal funds was largely responsible for the breakdown in the case-finding apparatus. Some students of the disease feared that the reduction of the prevalence of syphilis was more apparent than real. I, among others, emphasized the need for continued epidemiologic control of infectious syphilis.[15]

In addition to the handicaps from a loss of case finding, other factors conspired to expand the syphilis problem after World War II. The advent of ease and rapidity of obtaining a cure through the use of penicillin played an important part. Previously, the long course of metal therapy, untoward reactions to treatment, and the high cost of prolonged treatment placed it in the public health or university hospital clinics. Only a few patients having infectious syphilis were treated by physicians in private practice, and these were usually relatively affluent. Their loss to epidemiologic study was of little practical concern, since such patients were less likely to be widely promiscuous but rather had only an occasional exposure or a prolonged liaison with one sexual partner. The remainder of the patients met in private practice were commonly referred to the public clinics.

It was in these clinics that epidemiologic investigation was developed to a high degree of success in the control of syphilis in the pre-penicillin era. The movement of treatment of persons with acute syphilis from the public clinic into the private physician's office, where only several visits became necessary for the cure of syphilis, greatly hampered case finding and enhanced the breakdown of epidemiologic control which followed the curtailment of federal funds.

RECRUDESCENCE OF SYPHILIS

Even though the *cure* of syphilis became a biologic fact with a few injections of penicillin—and this short-term treatment assured its completion while interest and fear existed—and although a lessened incidence of infectious relapse resulted in a reduction of the infectious pool in a community, a rise in the incidence of syphilis became apparent in 1958.

The obvious lack of reporting by private physicians, who were now treating a large proportion of the patients having acute syphilis, had become suspect as a major factor in the *apparent* lessened prevalence of syphilis. Brown, Sellers, and Thomas[3] pointed to this in 1959. They found that in the years 1954 to 1958, 19,521 patients with infectious syphilis were reported from clinics and hospitals and that 86 per cent had been interviewed regarding contacts. In the same period, of 14,428 patients reported by physicians in private practice, only 17 per cent were interviewed regarding contacts. These 2400 patients upon interview provided 8000 contacts; if the remaining 12,028 *had been interviewed* they would have yielded, in terms of national indexes of case finding, 40,173 contacts, among whom there would have been 2868 cases of infectious syphilis, 1606 cases of early latent syphilis, and 594 cases of other types of syphilis. Clark[6] in 1960 estimated that the annual incidence of acute syphilis in this country was about 60,000. Yet the average number of reported cases annually was 6500 in each of the preceding five years, indicating that 53,500 probable cases of infectious syphilis remained unreported annually.

Since the upward trend in the incidence of syphilis continued through fiscal 1961 (Fig. 2), Surgeon General Luther L. Terry appointed a Task Force to survey the problem and make recommendations. Its report was completed in late 1961.[9] Not only did it emphasize the increased number of cases reported, but it also called attention to the alarming spread of syphilis among teenagers, with the statement that "between 1956 and 1960 there was a rise of more than 130 per cent in infectious syphilis among persons under 20 years of age." The Task Force was particularly disturbed by "(1) evidence of a chain reaction in the spread of syphilis infection, especially among teenagers; (2) evidence that the actual number of cases occurring far exceeded the number of cases reported; (3) evidence that effective techniques in the control and therapy to stop the spread of syphilis are available but not applied widely enough; and (4) evidence that unless a vigorous stepped-up program is inaugurated now, the increased spread of syphilis currently being observed may be accelerated."

The Task Force recognized that the control of syphilis was still unfinished business. It was also apparent that control or eradication was impossible without the help of private physicians, who quite clearly were treating more patients than were treated in the public clinics and were reporting only about a fourth of those treated. Studies of sex behavior, particularly among teenagers, pointed up the need for a new educational effort for the public.

RECOMMENDATIONS BY THE TASK FORCE

The Task Force made certain recommendations which have been implemented and are being expanded by the present chief of the Venereal Disease Branch of the U.S. Public Health Service.

INTERVIEW-INVESTIGATION TECHNIQUES. These techniques, applied by field investigators, had already improved to the point that two of every three patients with infectious syphilis who were interviewed yielded at least one contact with infectious syphilis. In addition the Georgia study demonstrated that on re-interview of contacts, 43 per cent named additional contacts.[3]

CLUSTER TESTING. This represents an extension of the interview to include not only sex contacts of patients, but friends or acquaintances with sexual behavior probably similar to the patient's and whom the patient thinks may benefit by examination. This method added a 24 per cent yield of infectious cases in a study carried out in fiscal 1961.

REVIEW IN EARLY LATENT SYPHILIS. Figures have shown that 1 of every 12 patients with early latent syphilis who is interviewed leads to one contact whose syphilis is infectious. This emphasizes the importance of this group of patients in maintaining infectious syphilis in the community, probably by unrecognized relapse.

ROUTINE SCREENING. The Task Force found that the 31,000,000 serologic tests for syphilis done annually in the country represented a screening of 10 per cent of the population each year, including 3,000,000 premarital tests and 4,000,000 prenatal tests. They found that some 1,200,000 of the 31,000,000 were reported as positive and that only 70 per cent of these patients were reported to health authorities, mainly by health departments and charity hospitals. This method of case finding is important and the Venereal Disease Branch is gradually gaining the cooperation of clinical laboratories in reporting positive tests.

EPIDEMIOLOGIC TREATMENT. In the past several years the Venereal Disease Branch has developed the philosophy that the optimal time to treat syphilis is during the incubation period. In a study of 1350 persons exposed to infectious syphilis during the previous 90 days, who were clinically and serologically negative on first examination, four groups were treated with penicillin, ranging from 2.4 million units downward, and a fifth group was treated with a placebo. In this study one of every ten contacts not treated developed syphilis within the next 90 days. Even though the patients who had been seronegative were followed as closely as possible, they had already reached the secondary stage when the diagnosis was established and had obviously been a hazard in the community. The study showed that the 2.4 million units of penicillin essential to the successful treatment of secondary syphilis is required as well to abort incubating disease.[21]

EDUCATION OF THE PUBLIC. In its report the Task Force pointed out that in 1960, 51,265 cases of infectious venereal disease (early syphilis and gonorrhea) were reported in persons under 20 years of age. Because of the under-reporting of gonorrhea particularly, it seemed probable that more than 200,000 cases of infectious venereal disease occurred in teenagers annually. In 1956 the infectious disease rate in persons 15 to 19 years old was 10 per 100,000 population; in 1960 it had reached 19.4 per 100,000.

A voluminous literature has accumulated dealing with the sociologic and attitudinal changes which have developed among the young in recent years, and even a summary would be impossible. Factors which are thought by many to play a role in the increase in venereal disease and illegitimate pregnancies in teenagers are laxity in morals, availability of the automobile and spending money, a generally negative attitude toward authority, lack of discipline and parental authority in home life, emancipation of women, earlier physical development, urbanization, and a host of others.[18, 26] Studies by Celia Deschin[7] of 600 teenage victims of venereal disease are particularly revealing. These children did not necessarily come from broken homes. Truancy was great among the teenagers who knew little of venereal disease. The major source of sex knowledge for 54 per cent of them was their friends; parents were the source of such knowledge in only 21 per cent. Promiscuity was less likely if the child had a positive identification with parents or adults for such knowledge. The number of dropouts from school was high in this group. Particularly revealing to me was Deschin's statement that in answer to her question of what this group of young people did with their spare time, 50 per cent of the 600 answered, "Nothing." For what type of citizen can one hope if in youth there are no meaningful or socially useful responsibilities!

Thus accumulating knowledge emphasizes the need for a dynamic approach to the education of the teenager in regard to promiscuity and venereal disease. It is clear that the home and the church are not dependable sources of such teaching. The challenge has been met very well in some areas by school systems, the only dependable stage from which sex education may be disseminated.[8]

PROFESSIONAL EDUCATION. It has already been indicated that the rising incidence of syphilis coincided with the movement of antisyphilitic treatment into the office of the private physician.[3] By their own admission, in a questionnaire covering a three month period (April 1 to June 30, 1962), private practitioners reported to health departments only some 10 per cent of patients having infectious venereal disease.[25]

It is quite obvious that the medical profession must be made to realize its great responsibility in the eradication of syphilis, first, by reporting cases of infectious venereal disease, and second, by cooperating in contact investigation through the introduction of the private patient to the venereal disease investigator. It must be known that syphilis can never be controlled so long as only the minority of patients with infectious disease are reported and if epidemiologic control is not applied.

Though well justified criticism has been directed at the practicing physician, I, as a teacher, as a consultant practitioner, and as one reasonably well versed in public health objectives, must recognize the logical reasons for the practitioner's apparent lack of cooperation.[16] In his background, by education and training, the doctor has had inculcated the attitudes and philosophies of the Hippocratic Oath, an ethic maintained over the centuries and as basic for the good of the patient today as two millenniums ago. Furthermore, lukewarm cooperation by the doctor may be enhanced at times by attitudes of health departments in their dealings with a community's medical profession, as well as by ignorance resulting from curricular deficiencies and from responsibilities of deans and chairmen of departments in today's medical schools.[34]

There have always been many physicians who have recognized their responsibility and have gone out of their way to aid in contact investigation. This we know from experience over the years. Actually, one of the earliest epidemiologic studies (1932) was carried out with private practitioners.[22] On the other hand, a large segment of the profession has not faced its responsibility for one of three reasons. The first is a complete lack of motivation in some, who merely answer a plea or an argument for cooperation in contact investigation with, "I am too busy to do this." The second objection to such a plea has its basis in the principle of privileged information between patient and physician, so ingrained in all phases of medical education and practice that by second nature the doctor hesitates to divulge confidential information about a patient to anyone, particularly to a public agency or a layman. Furthermore, liability suits or threats thereof appear almost daily in any medical community today; the only reason there have been few suits involving venereal disease is that the plaintiff is unlikely to admit publicly that he is a victim of such a disease, because of its nature.

Education of the medical profession to its responsibility in venereal disease control must take into consideration these deterrents to even an interested physician. That these established concerns can be overcome successfully by education has been demonstrated by a three year study in Georgia, begun in 1956, as reported by Brown and his associates.[3] Following a program of education of the profession, which included the introduction of trained interviewers to their patients, ten times more cases of syphilis were reported, and the number of patients interviewed increased 97 per cent in this period, as compared to the three years immediately preceding this program.

Nevertheless, education of the medical profession must be expanded. The American Medical Association, through its *Journal*, its *PR-Doctor*, and excellent articles in *Today's Health*, as well as the National Symposium on Venereal Disease held in Chicago in November, 1965, has contributed its share in this area. The public health departments collectively will contribute immensely by the program of having their venereal disease investigators make two visits annually to 100,000 general practitioners and one each year to the remaining 130,000 physicians in practice. Thereby, the "trained" interviewer may demonstrate to the practitioner that he has the attributes essential to success in contact investigation. In the last analysis the patient holds the key to case finding, and the interviewer must be sensitive to the differences mentioned previously, which set off the average clinic patient from some in the private patient category. This means that he needs to be sensitive to the patient as a person and to all the implications of doctor-patient relationships, and must be the guardian of all manner of confidences involving the patient. The least misstep may shatter the cooperation of the private physician, obtained after much persuasion against all the tenets of protecting the patient.

Another reason for some practitioners' apparent lack of cooperation with public health departments harks back to serious deficiencies in his undergraduate medical education. He may find himself in a quandary and not know which way to turn; he knows what he *should* do but does not know *how* to do it. The circumstances are that the physician finds acute syphilis in a spouse, and fearing or recognizing the family turmoil which may result, he rationalizes that keeping the family intact may be more important than doing something about the disease.[29] On a number of occasions physicians in this dilemma have thrown the problem into my lap as a consultant because of their fear of the consequences if they moved in the direction that they knew was necessary. As I review my decades of experience with physicians I have concluded there are several reasons for their *apparent* disinterest in the epidemiology of syphilis. In the first place, they have given little thought to the epidemiology of the disease; this is particularly true of the more recent graduate than of one who received his degree before World War II. The graduate of the days of prolonged metal therapy and case finding, reinforced by his experiences as a medical officer in the armed forces during the war, was left with knowledge and impressions that he will never forget. He needs little education in epidemiology but in how to meet the problems mentioned above. On the other hand, undergraduate instruction in the venereal diseases has been so woefully poor in the years subsequent to the war that one encounters abysmal ignorance of these diseases in recent graduates.

Another and very cogent reason for physicians not to pursue their responsibilities in obtaining names of contacts and other information is that some find themselves speechless when faced with the need of exploring a patient's sex life, particularly if the patient is a female. Again this is a reflection of inadequate instruction as an undergraduate or even as a graduate student. (This deficiency is currently receiving attention in several fields of medical education.[27]) Embarrassment and ignorance are enhanced by the physician's upbringing in attitudes about sex in his home environment. The taking of a history relative to homosexual and so-called "unnatural" sex practices is so repugnant to many a physician, in terms of his "moral upbringing," that his contact investigation is extremely limited. Relatively few physicians either ask or know how to ask about other than accepted heterosexual practices, and thereby their histories in cases of infectious syphilis are wholly inadequate in terms of some current problems. Sexual experimentation in the teenage population especially may extend beyond generally accepted sexual mores, and the doctor may be completely lost in his attempt to explore the sex life of today's youth.

Thus, in facing the reactions of private practitioners to requests for collaboration in contact investigation, one may encounter, on the one hand, attitudes which in some are frankly obstructive, but which in most instances represent sincere bafflement as to what to do. On the other hand there is an ignorance of the importance of epidemiologic investigation and deficiencies in medical education. Nevertheless, since the key to the eradication of syphilis lies in the hands of a practitioner too busy or untrained in the necessary field work in contact investigation, reliance must be placed upon the trained investigator. Increasingly, the doctor is being educated to accept the investigator, a layman, in sharing the responsibilities in epidemiologic control of syphilis. Figure 3 illustrates the results of cooperation between practitioners

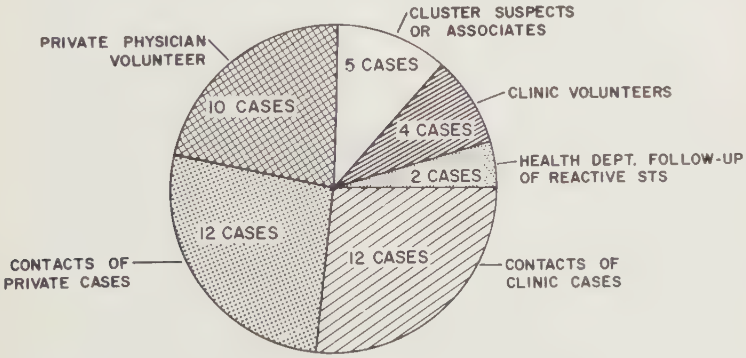

Figure 3. Reason for examination in 45 cases involved in epidemic. (From Ball,[1] Venereal Disease Control Section, South Carolina State Board of Health. Courtesy J.A.M.A. *193*:101, 1965.)

and the health department in a small southern city served by 11 private physicians, in which an epidemiologic study involved 365 white persons in five counties and eight states.[1] Fifteen doctors reported 26 cases and examined many of the contacts. The 26 private patients provided 124 sex contacts; the 19 public clinic patients provided 101!

PROBLEM AREAS IN EPIDEMIOLOGIC CONTROL

Though the methods for syphilis control have been established and are being extended, and though the education of the profession is making progress, there remain two areas about which one may have doubts as to the attainment of maximal epidemiologic control. The recognition of these two segments of the population are of exceptional importance to the doctor who encounters a positive blood test in a patient in the hospital or his office. In both groups the patient in all honesty may be unaware of having had acute disease, or, if it occurred, may have misinterpreted symptoms in all ignorance, and lastly he may refuse to reveal information because of other than accepted modes of sexual intercourse.

The Teenager

The first of these two populations is the teenage one, already alluded to in some detail because of the disproportionate increase in venereal disease in this group.[24] Though in urban areas through case finding and cluster testing, based mainly on public clinics, many infected teenagers are identified,[33] I question the extent of successful case finding in the better socioeconomic levels and in smaller or rural communities. Consider the following case of an 18 year old girl of excellent family background.

This girl visited a student health service because of a painless vulval lesion which had been present for 3 weeks. She denied to me, as a consultant, any genital contact but had permitted cunnilingus with one of her "dates" upon occasion; such episodes, after a 10-week period of abstinence, last occurred 3 weeks before I examined her. The small hymenal opening was intact. On the labial aspect of the left labium majus was a clean, infiltrated ulcer 1 cm. in diameter, and darkfield-positive; the sentinal inguinal node was enlarged and tender. Serologic tests were positive.

Had this girl not had the intelligence, good sense, and courage to consult a physician, one might speculate upon her later history. (The lesion would have healed in another week or so.) Unless overt secondary syphilis had driven her to seek medical help, she might have been found, upon premarital testing some years later, to have a positive blood test and upon examination an intact hymen. Upon superficial questioning, her doctor might have accepted her statement that she had never had "sexual intercourse." He might have then dismissed the serologic test as "falsely positive!" Or if she married a year or two after exposure, in a state not requiring premarital blood tests, and delivered in a small community hospital not requiring prenatal blood tests, she might have been delivered of a syphilitic infant, or had a miscarriage. Or if, as a spinster many years later, she had developed a form of late syphilis, and upon examination was found to be a "virgin," she would present an enigma to her family physician. Any consultant in syphilis can document similar instances revealed by an adequate history.

My fear then is that if the estimates are correct that at least 25 per cent of infected patients remain untreated, common sense dictates that this percentage is probably higher in the female teenage group. Again I must emphasize public education for both prevention and diagnosis and treatment, and professional education to "know syphilis," in Osler's words.

The Homosexual

The second problem in epidemiologic control concerns homosexuality and its contribution to the spread of venereal disease, particularly in the male. The biologic phenomenon of homosexual contact is common among both sexes in all infrahuman species of mammals. Homosexuality was recognized in ancient literature, and in early religions, later to be condemned. The taboos and mores of primitive peoples document its presence. The literature of the past several centuries identifies homosexuality in well known authors, artists, and public figures. However, no one had any conception of the prevalence of homosexuality in the male until Kinsey and his group[19] concluded that about 50 per cent of the male population is exclusively heterosexual throughout adult life, that 4 per cent is exclusively homosexual throughout life, and that almost one half or 46 per cent have both heterosexual and homosexual activities in their adult life. They admitted to being unprepared for such statistics, and they checked and rechecked population groups, finally accepting their figures.

Whether the prevalence of homosexuality is greater today than a generation or a century ago is unknown. All that is known is that the past six to eight years have contributed a large scientific literature on the many social and anthropologic aspects of homosexuality, the peculiarities which surround its practices, and its role in the spread of venereal disease. (Contributions come from all the Western countries.) Some believe homosexuality may be more prevalent because of teenage experimentation, being the "thing to do," and urbanization. Others believe an increase is more apparent than real, representing less secretiveness by homosexuals as the prevalence of homosexuality is more generally recognized. Whatever the explanation may be, to those of us who were involved in the epidemiology of syphilis in Nashville 25 years ago, the chain of infection in this city for 1963, shown in Figure 4, is utterly fantastic. We and others of those days apparently assumed that heterosexual contacts ruled out homosexual exposure, although why we did not stumble onto the truth still seems inexplicable. The problems in epidemiologic control in a homosexual population may be summarized by citing studies in one geographic area.

The sociologic study by Evelyn Hooker[11] shows that homosexuality involves a rather characteristic pattern of life and customs. From an intensive study of a small group of homosexuals in Los Angeles, whom she interviewed and re-interviewed carefully over a period of several years, it appears that the majority of homosexual contacts are limited to one episode with one sexual partner, which accounts for the homosexual's tremendous promiscuity. The reason for this pattern is the great need for anonymity, actually a nonidentification of self to one's partner, resulting commonly in a sincere inability of the homosexual to identify his partners. Anonymity is imperative in the "gay" world to reduce the probabilities of being recognized and coming up against legal, social, or economic sanctions, and to avoid blackmail, which is

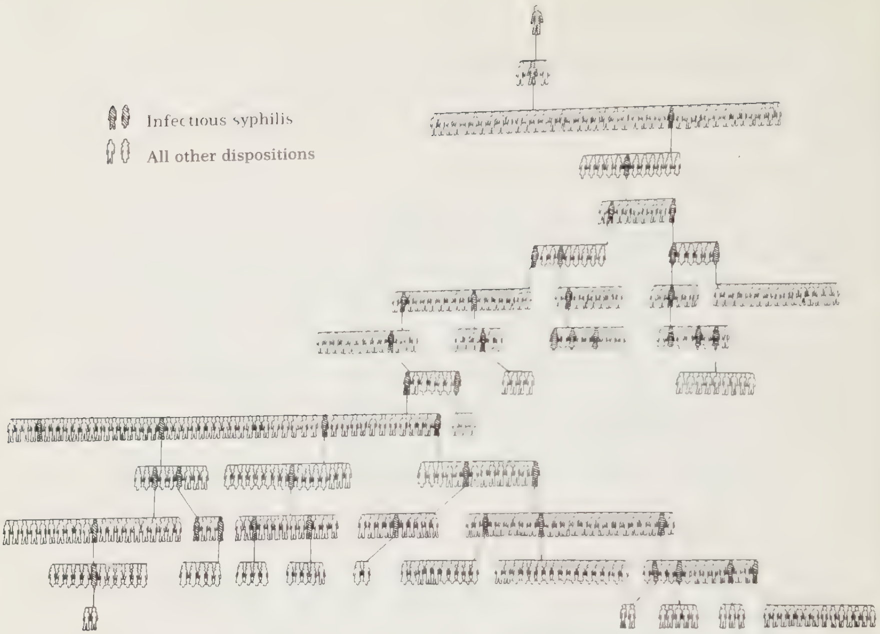

Figure 4. This chain of infectious syphilis began in May, 1962, with one homosexual patient who voluntarily entered the Health Department of Nashville. As a result, 47 infected persons were identified. The total of named contacts was 446 for an average contact incidence of 10.37; 438 or 98 per cent were located and brought to examination. In addition, by cluster testing, 452 suspects and associates were also examined, with a yield of 7 cases of infectious syphilis and 15 cases of gonorrhea. (The total number of persons examined was 898; they represented a lower socio-economic class and were biracial.) In this epidemic 47 per cent of the males admitted to homosexual practices. (From the Davidson County Health Department, Nashville, V.D. Investigators, Robert Flye and Thomas Gray. Courtesy, Tennessee Public Health Quarterly Bulletin *12*:1, July–Sept., 1963.[30])

particularly likely for a married man who becomes involved in homosexual practices. In California, homosexual activities are a crime before the law. The armed forces attempt to avoid recruitment of homosexuals and, upon the identification in service, discharge them as having "undesirable habits or traits of character," officers being offered resignation of their commission. These and many other kinds of social and economic sanctions conspire for nonidentity. Male prostitutes play a small role, contacts being casual and picked up in "gay bars," "steam baths," theaters, and parks—"one-time" contacts for the traveling man or other transient.

The magnitude of the contribution of the homosexual to the spread of venereal disease has become evident only in recent years, and figures vary. The Joint Statement[12] of 1962 demonstrated that reporting from 33 states and 64 cities showed an increasing evidence of venereal disease in homosexual men. Tarr and Lugar[31] reported a study made in Los Angeles in 1959. Of 194 persons with infectious syphilis diagnosed in the city health department, 170 (87.5 per cent) were male and all but 11 named more than one contact. Of these 159 males, 89 or 56 per cent named only male sex contacts, 21 or 13.2 per cent had had both male and female contacts, and 49 or 30.8 per cent named only female sexual partners. The 89 males who had only homosexual relationships named 551 sex contacts, an average per patient of 6.26 (contact index); the 49 who had only heterosexual contacts identified 137 partners, a contact index of 2.79. In this study at least, promiscuity was much greater in the male homosexual population. Among the 551 named contacts of the 89 men who were exclusively homosexual, 93 had infectious syphilis.

On the other hand, in Evelyn Hooker's[11] careful sociologic study of 90 homosexuals, syphilis had been acquired by only three, though half of the men had had gonorrhea (urethritis or proctitis), some as often as five times. One of the three was 42 years old and estimated 1500 different male partners over 15 years; he had gonorrhea only once and acquired syphilis only in recent years. The incidence of venereal disease obviously is dependent upon its introduction into a given segment of a population. The preferences in homosexual practices may play a part in the likelihood of acquiring syphilis. (In Hooker's core group of 30, 16 per cent prefer fellatio and never take part in sodomy; 43 per cent prefer fellatio but will on occasion take part in anal intercourse; 23 per cent have no preference, engaging in either activity; 16 per cent prefer the dominant role in sodomy, but will practice fellatio.) There seems to be evidence that anal exposure has a greater hazard in the acquisition of venereal disease.

Thus, the second problem area in epidemiologic control has been emphasized – a problem area because homosexuality must have a large element of anonymity and one-time exposure, resulting in a promiscuity not equaled by heterosexuals. It is a topic about which the practitioner of medicine knows little and for him a case report may emphasize a diagnosis problem.

A 20-year-old student developed malaise, aching, low grade fever, and then a chill with a temperature of 105°, which led to hospitalization. The patient developed these symptoms several days after returning to college from a holiday, driving in company with another student who "came down with the flu." A system review in the hospital revealed the patient had become aware of constipation one to two weeks previously, with a sense of being unable to empty the rectum that was relieved by enemas. Three days before admission he had noticed some blood on the toilet tissue.

Examination showed evidence of pharyngitis. The palpating finger found a mass involving the anterior rectal wall with a crater estimated to be 3 to 4 cm. in diameter. Proctoscopy confirmed the rectal mass and a necrotic ulcer which was negative to darkfield examination. (The patient had received 5 doses of erythromycin, 250 mg. each, for the acute symptoms which subsequently led to hospitalization.) The VDRL test was reported as positive in 2 dils; following 7.2 million units of penicillin it rose to 16 dils in one week. The mass became resolved; the ulcer healed, as shown by proctoscopy, in two and a half weeks, and the VDRL test was negative. The patient denied heterosexual contacts, but admitted homosexual acts since age 14, having his first rectal exposure some 9 months before entering the hospital; in the 3 months preceding admission he had been exposed once or twice weekly to the same person.

Had this young man not developed an intercurrent acute respiratory infection, the student health service would not have had the opportunity to hospitalize him, the rectal symptoms would have subsided spontaneously, and unless overt secondary manifestations had forced medical attention, an attending physician possibly years later might have been nonplused by a positive blood test or late syphilitic disease in one denying a genital lesion and heterosexual contacts before marriage – if he married. The epidemiologic inferences are obvious.

CONCLUSION

Forty-four years ago, as a medical student, I spent a portion of the summer on treatment wards at the State University of Iowa, which were established by legislation as a result of a crusade against the social diseases by Secretary of the Navy Josephus Daniels during World War I. Here I injected neoarsphenamine, policed patients in their daily mercury inunctions, supervised the irrigation of male urethras with solutions of potassium permanganate and the instillation of a solution of an organic silver salt, and treated the cervix and vagina with Mercurochrome and instilled a solution of silver salts into the urethra. In 1936, the year that Surgeon General Thomas Parran began his attack upon syphilis, I was placed in charge of "Medical L" of the Department of Medicine at Vanderbilt University School of Medicine. In the following year this clinic began an active role in training personnel for venereal disease control in the South. Later it played a part in the evaluation of penicillin for the treatment of syphilis under the auspices of the National Research Council.

Is it not ironic that now, a quarter of a century after the beginning of what for a time *seemed* successful control, the citizens of all countries again face the identical problems of those early years?

Is it not of interest that an infectious disease with sharply defined modes of spread, one for which there is very effective treatment in most instances, and one therefore that should be easily controlled, should still offer itself as an unsolved problem?

Is it not of interest that the very advances of medical science have complicated immensely the control of diseases which go hand in hand with sexuality, which in itself seemingly has been enhanced by almost revolutionary social changes and attitudes?

The ease and success of antisyphilitic treatment in the practitioner's office has dulled the tool of epidemiologic control. The fear of penicillin-resistant strains of gonococci is not negligible.

Only intensive education of the public and the medical profession can re-establish epidemiologic control of syphilis. (It is too early to comment upon an *apparent* leveling off or slight break in the incidence of reported syphilis in recent months.)

The continuing search for new antibiotics effective against the gonococcus, if successful, can meet the threat of penicillin resistance. However, that search will never end, for strains will become successively resistant to new antibiotics.

Finally, one can only hope that current investigations may be successful in the development of an effective treponemal vaccine.

Irrespective of any and all developments, and the venereal diseases being what they are, the need for their constant surveillance has been clearly demonstrated by events of the past two decades.

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Tuberculosis and BCG

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After the Second World War an essential part of the fight against tuberculosis in Europe consisted of the use of large-scale BCG vaccination campaigns. These campaigns were not carried out according to strict scientific principles since the circumstances did not permit the inclusion of unvaccinated control groups. However, the results of animal experiments and a few promising small-scale trials in humans caused the organizers of these campaigns to be so convinced of the value of BCG vaccination that they took the, one may well say, audacious step and went ahead. Subsequent studies with suitable controls on the efficacy of BCG vaccination indicate that their decision was justified.

In the United States of America mass vaccination with BCG has been used to a limited extent only, partly because of the low protection observed after the campaign in the Southern States around 1950.[21] A re-evaluation of that material has recently been made by Comstock and Palmer[6] after an observation period of 14 years. Their conclusion is that the fight against tuberculosis in the U.S.A. should be concentrated mainly on the tuberculin reactors, with chemoprophylaxis of apparently healthy carriers of tubercle bacilli, especially among those reactors whose risks are known to be high. It is also stated that the risk of tuberculosis among nonreactors is too low to justify the use of BCG vaccination of that group.

I have not mentioned this work in order to start an argument about the tuberculosis program in your country. Assessment of the epidemiological situation involves many considerations, especially in countries with a low incidence of tuberculosis, with an effective Public Health Service, and with good treatment facilities. I mention it merely because of the poor results of the BCG vaccination in this trial. The authors'

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Table 1. *Vaccination of Large Population Groups*

PROJECT	NO. OF PERSONS	INCIDENCE
U.S. Publ. Hlth. Service[6, 21]		
Control group	17854	0.128
BCG-vaccinated	16913	0.110 (14%)
Brit. Med. Res. Council[3]		
Control group	12867	1.91
BCG-vaccinated	13598	0.40 (80%)
India[11]		
Control group	5808	4.99
BCG-vaccinated	5069	2.17 (60%)

conclusion is: "The evidence indicates that the protection afforded by BCG in this population was less than modest, relatively short-lived, and least effective among the segments of the population who needed it most."[6] These results are in contrast to what has been found in other well-controlled trials involving *mass vaccination* with BCG as well as in studies on vaccination of more limited groups with a *high exposure or a high infection risk to tuberculosis.* Some of these studies are described in the following.

BCG VACCINATION OF LARGE POPULATION GROUPS

Table 1 shows a few details of the Public Health Service project in the Southern United States[6, 21] as compared with two other studies dealing also with vaccination of large population groups: The English trial published by the British Medical Research Council[3] and the Indian published by Frimodt-Møller et al.[11]

The observation periods were 14 years, 9 years and 10 years respectively and the criterion for vaccination was: no reaction to 5 tuberculin units (TU) in the American and Indian study and in the British study no reaction to 100 TU. As can be seen, the reduction in the incidence of tuberculosis among the total number of vaccinated was only 14 per cent in the American study. In the British study the reduction in the number of cases amounted to about 80 per cent and in the Indian study to about 60 per cent.

BCG VACCINATION OF POPULATION WITH HIGH EXPOSURE RISKS

The next studies I shall mention concern the value of BCG vaccination in population groups with high exposure risks. Table 2 shows Aronson's study[1] of the North American Indians in 1946. The criterion for vaccination was no reaction to 0.005 mg. PPD and the observation period was six years. As can be seen, the reduction in the number of cases was again about 80 per cent. Furthermore, there was no indication that the immunity decreased with the passage of time after vaccination.

Table 3 shows another example of the efficacy of BCG vaccination on the incidence of tuberculosis in environments with particularly high infection risks. That is the pioneer study of Heimbeck[13, 14] consisting of

1927 vaccinated Norwegian nurses in the Ullevål Hospital in Oslo. The criterion for vaccination was no reaction to the Pirquet test. The table shows the results during the first three years in hospital, the probationary period. The reduction in morbidity was about 80 per cent. This study demonstrates quite clearly the dramatic effect of BCG vaccination on the morbidity of tuberculosis in an environment which certainly is a very dangerous one for tuberculin-negative nonvaccinated persons.

Still another example of the good protective effect of BCG vaccination in a heavily exposed group was observed in a TB epidemic which took place among pupils in a secondary school in Denmark in 1943. It was the subject of a study reported by Hyge[15] based on a follow-up observation period of 12 years.

The story is as follows: A case of tuberculosis occurred in one of the pupils and consequently examinations and BCG vaccinations were carried out in the school. All pupils who did not react to 100 TU were BCG vaccinated. At the beginning of the new school year a group of nonvaccinated, tuberculin-negative children were enrolled, and thus by chance a material became available which resembled that of a well-planned experiment. It should be mentioned that the case of tuberculosis which occasioned the BCG vaccination had no connection with the epidemic which occurred 16 months later but was caused by a teacher with an undiscovered case of pulmonary tuberculosis.

The disease spread with explosive haste in certain classes which were especially exposed because their instruction took place in a blacked-out air raid shelter. As shown in Table 4, there were 94 tuberculin-negative and 106 BCG-vaccinated children in the classes. Of the

Table 2. *Vaccination in a Population Group with High Exposure Risk. North American Indians* (Aronson[1])

	NO. OF PERSONS	INCIDENCE
Control group	1457	24.3
BCG-vaccinated	1550	4.7 (80 %)

Table 3. *Vaccination in an Environment with High Infection Risk. Hospital Nurses* (Heimbeck[13])

	NO. OF PERSONS	MORBIDITY
Control group	284	141.2
BCG-vaccinated	501	24.1 (80%)

Table 4. *Tuberculosis Epidemic in a School* (Hyge[15])

	CONTROLS	BCG-VACCINATED
No. of pupils	94	106
No. infected	70 (75%)	–
Primary tub.	41 (44%)	0
Post-primary tub.	14 (15%)	2 (2%)

nonvaccinated 75 per cent became infected, 44 per cent developed primary tuberculosis, and 15 per cent post-primary tuberculosis. None of the BCG-vaccinated children developed primary tuberculosis and only 2 per cent post-primary tuberculosis. In this school outbreak the BCG vaccination thus gave complete protection against primary tuberculosis and reduced the number of post-primary cases by almost 90 per cent during an observation period of 12 years.

These are only a few examples of the many accounts concerning BCG and are well known to many, but are mentioned because in this era of chemotherapeutics it should be emphasized that BCG vaccination can be of tremendous value in a number of different epidemiological situations.

DIFFERENTIAL CHARACTERISTICS OF VARIOUS BCG SUBSTRAINS

The striking difference between the poor results obtained in the vaccination campaign in the Southern United States and the satisfactory results obtained elsewhere makes it natural to search for an explanation of the conflicting observations. In this connection I would like briefly to mention some recent laboratory data on differential characteristics of various BCG substrains since these data most likely have a bearing on this problem.

I shall deal mainly with studies on the Chicago and Albany strains which were used with disappointing results in the Southern United States[6] and Puerto Rico[21] as compared to the Philadelphia strain used by Aronson[1] in the successful trial in the North American Indians.

BCG strains possess three characteristics by which their potency can be measured quantitatively in laboratory animals. These are (1) virulence, (2) capacity to evoke tuberculin sensitivity, and (3) ability to induce resistance to infection with virulent tubercle bacilli.

1. As regards *virulence*, the Chicago and Albany strains have been compared in many experiments and by different techniques with the Philadelphia strain. Thus Suter and Dubos,[24] Pierce et al.,[22, 23] and Willis et al.[25] all found that the Philadelphia strain has a significantly higher virulence than the Albany and Chicago strains. As shown in Figure 1, similar results have been obtained by Jespersen,[17, 18] who determined the survival time of hamsters following intraperitoneal

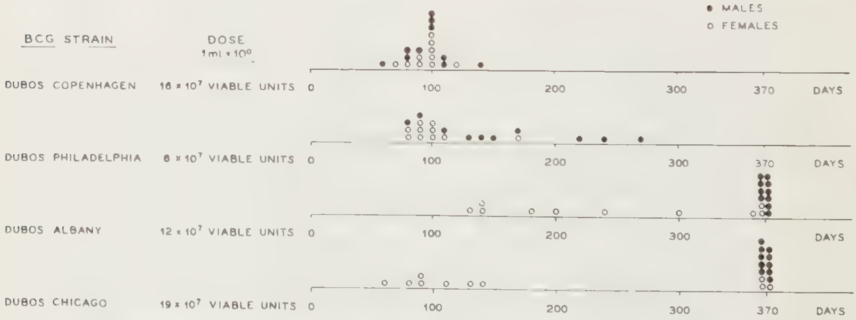

Figure 1. Survival time (in days) of golden hamsters inoculated intraperitoneally with living vaccines produced from various BCG strains.

inoculation of large doses (1 mg.) of four different strains of BCG. As can be seen, the Philadelphia strain had a strong lethal effect on the hamsters, both females (open circles) and males (black circles) to the same extent as the Copenhagen strain. On the other hand, the Chicago and Albany strains were both weak and killed only a few of the female hamsters.

2. The capacity of the strains for evoking *tuberculin sensitivity* has been compared in studies on guinea pigs by Willis et al.[25] In these experiments the Philadelphia strain induced a greater and more persistent tuberculin sensitivity than the Chicago strain. The Albany strain gave intermediate results.

3. *Protection experiments* have been carried out in white mice, red mice, and guinea pigs. In comparative studies on the capacity of various BCG strains to inhibit multiplication of virulent tubercle bacilli in the organs of white mice, it was shown (Dubos and Pierce[7]) that the acquired resistance declined progressively up to the seventeenth week in mice vaccinated with the Chicago strain, whereas it remained at its maximal level in those vaccinated with the Philadelphia strain.

Figure 2 shows a study by Jespersen and Bentzon,[19] who used red mice to measure resistance after vaccination with varying doses of BCG vaccine. Five weeks after vaccination the mice were challenged intravenously with virulent tubercle bacilli and the survival time was used as indication of resistance.

The median survival time is shown on the ordinate and the dose of vaccine on the abscissa. The animals vaccinated with small and medium doses of the Philadelphia strain had significantly longer survival times than those given corresponding doses of the Chicago and

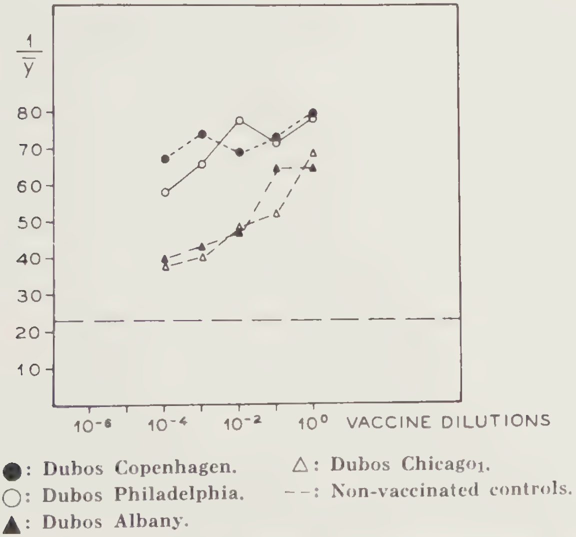

Figure 2. Protection experiment in red mice. Relationship between the median survival time $\left(\frac{1}{\bar{y}}\right)$ and the dose of vaccine. (Reproduced from Jespersen, A., and Bentzon, M. W., Acta tuberc. scandinav., 1964.[19])

Albany strains. In this study there was no significant difference between the latter two strains.

Willis et al.[25] have determined the acquired resistance in guinea pigs. With long-term vaccination the Chicago strain gave no significant protection, while the resistance induced by the Philadelphia strain was high. The effect of the Albany strain was intermediate.

The laboratory data thus show clearly that there are significant differences between BCG strains which can be measured in experimental animals. The importance of these differences was emphasized by Jensen,[16] Dubos et al.,[7, 22, 23] and also by Willis and Vandiviere,[26] who concluded that there is a close relationship between the results of BCG vaccination of humans and the protective effect in animals using the same strain, and that differences between strains can "explain, in part at least, the diverse claims that have been made in respect to the immunizing properties of what, until now, has been considered to be a product of uniform quality."

This conclusion is in good agreement with our experimental results and our experience with the Danish BCG strain, which, as mentioned, gave a very satisfactory protection in the British mass vaccination campaign.[3] This vaccine strain has been carefully studied in animal experiments at our institute by Jespersen and others over a period of more than ten years and has been found consistently to induce a high degree of resistance in red mice and in guinea pigs. There is with this strain a good correlation between its immunizing capacity in laboratory animals and its protective effect in humans.

Returning now to the problem of the low protection afforded in the BCG vaccination campaign in the Southern United States, it seems justifiable to conclude that the Chicago strain was greatly attenuated and that the Albany strain was less potent than the Philadelphia strain at the time they were used in the Georgia-Alabama and Puerto Rico programs. Even though the animal experiments have not been performed with the same batches as those used in the vaccination projects in question, this conclusion is most likely valid. The divergent findings of Aronson on the one hand, and of Palmer et al. on the other, can thus be explained as due to differences in the BCG strains employed.

The problem of selecting suitable strains for vaccine production is still of great importance and work in this direction is still going on. An international collaborative study has been organized by WHO and several strains are being examined, some of which will eventually be recommended as seed-lots for the production of BCG vaccines.

EXPERIENCE WITH BCG VACCINATION IN DENMARK

The vaccine used in Denmark is produced by the BCG Department of our institute from a substrain which, as mentioned, has been found effective both in animals[17, 18, 19] and in vaccination trials in humans.[3]

The first county in Denmark to include BCG vaccination systematically in the antituberculosis program was the island of Bornholm, which has a population of about 46,500. In 1936 the dispensary there offered vaccination to all nonreactors to tuberculin from tuberculous environments and to all young people about to leave the island, which has an isolated location in the Baltic Sea. The latter procedure was adopted because young tuberculin-negative persons often returned to the island with tuberculosis, having been exposed to the greater risk of infection in other parts of the country, especially Copenhagen. It should be mentioned that tuberculosis of cattle was eradicated on Bornholm in 1935.

Figure 3 (Olsen[20]) shows the age distribution of 134 newly registered cases in the five-year period before BCG mass vaccination was initiated on Bornholm. The highest incidence is clearly among young adults. This figure should be compared with Figure 4, which shows the age distribution of 82 fresh cases in the following five-year period, i.e., after the BCG vaccination had been carried through in all schools and among young adults. As can be seen, the incidence of TB had declined very considerably in the age group 15–35 years, i.e., in the group in which the greatest number of vaccinations had been performed.

In Copenhagen, BCG vaccination of children leaving school began in 1943–1944, and in 1946–1948 a mass survey and vaccination of the city's population were carried out. In 1949 a law was passed offering BCG vaccination to all tuberculin-negative children before leaving school. Subsequently it became the practice to offer BCG vaccination during the first year at school. Vaccination of preschool children and adults began on a nationwide basis in 1950–1952. There is no accurate figure available concerning the number of vaccinated persons in Denmark, but it is probably about 2 million, i.e., about 40 per cent of the population. In connection with these mass vaccination campaigns and the subsequent follow-up studies, the Danish Tuberculosis Index (DTI) was established in 1950. The aim of this institution was to provide possibilities for long-range, nationwide studies of the epidemiology of tuberculosis. Since then the tuberculosis dispensaries have notified systematically to DTI all details concerning their patients. The Tuber-

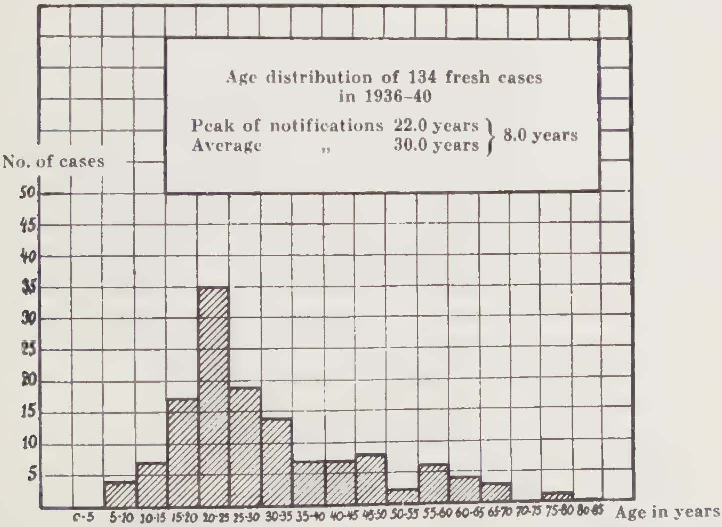

Figure 3. Age distribution of fresh cases of tuberculosis in the period 1936–1940, when BCG vaccination was started, but chiefly only in tuberculous environment. By the end of 1940, 2394 persons had been vaccinated. (Reproduced from Olsen, H. C., Acta tuberc. scandinav., 1953.[20])

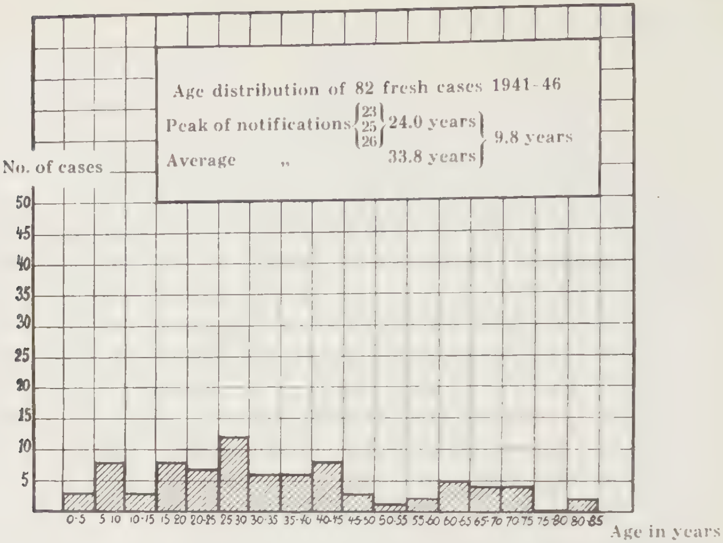

Figure 4. Age distribution of fresh cases of tuberculosis in 1941–1945, when BCG vaccination was carried through all schools, children's homes, the military forces, home-guard institutions, etc. By the end of 1945 a total of 10,337 persons had been vaccinated, about 23 per cent of the population distributed mainly over school children and young people. (Reproduced from Olsen, H. C., Acta tuberc. scandinav., 1953.[20])

culosis Department of Statens Seruminstitut, the central laboratory for Denmark, also collects information regarding cases where tubercle bacilli are demonstrated.

The material from Bornholm[20] illustrates how BCG vaccination has affected the incidence of tuberculosis in a Danish county. Some details concerning the effect of the vaccination of school children in Copenhagen, with about 1 million inhabitants, compiled in 1964 by the chief of the Copenhagen Dispensary, Ole Christensen,[4, 5] are presented in Figure 5. They show the annual number of newly notified cases per 100,000 on the ordinate, divided into two age-groups 0–8 years shown by the white columns, and 9–14 years the black columns. These represent the years 1938 to 1962. Up to 1948 the incidence in the two age-groups was almost the same. From 1948 to 1949 there was a definite drop, probably because of the elimination of the sources of infection which were revealed at the time of mass vaccination. The effect of vaccination of all the tuberculin-negative school children from 1949 onward can be seen from the consistently lower incidence in that age-group—about one-third of the incidence in the preschool age.

PRESENT STATUS OF TUBERCULOSIS AND FUTURE BCG VACCINATION POLICY IN DENMARK

Information concerning the vaccination status in the Copenhagen schools in 1964–1965 has been provided by the chief school physician, A. Biering.[2] The total number of pupils was about 70,500. Of these 43 per cent were vaccinated before entering school and about 47 per cent after the age of 7 years. Of the children who had been BCG vaccinated previously, only a few (323) were tuberculin-negative and the majority of these were revaccinated. Only a small group of the children (about 6000) had not been vaccinated. Among the tuberculin-negative children, 23 became positive spontaneously either with or without the demonstration of tubercle bacilli, i.e., 0.4 per cent of the total number of unvaccinated children. Pulmonary tuberculosis was found in two children and in these newly diagnosed cases tubercle bacilli were demonstrated.

The frequency of positive tuberculin reaction in unvaccinated children outside Copenhagen has been studied by Birthe Groth-Petersen.[12] She found that in 1954, 4.1 per cent of the unvaccinated children in the first class were tuberculin-positive, while in 1960–1961 there were only 0.6 per cent. An examination by Engbæk et al.[8] in 1962 in a central school outside Copenhagen showed that, of 70 unvaccinated pupils in the three first classes, only one showed a positive reaction to human tuberculin.

The annual incidence of tuberculosis in Denmark is low (in 1963 about 18 per 100,000) and many of the cases are not due to new infection but to recurrence of the disease. This development naturally raises the question as to whether mass vaccination should be gradually discontinued, as advocated by Wallgreen in Sweden, and others. The tuberculin test would then regain its diagnostic value. However, we do not plan such a change in vaccination policy. Mass vaccination of school children will continue, as will vaccination of tuberculin-negative adults.

One argument for this policy is that even though the exposure risk is much less than earlier, tubercle bacilli are still isolated from a considerable number of new patients each year; in 1965 the number was

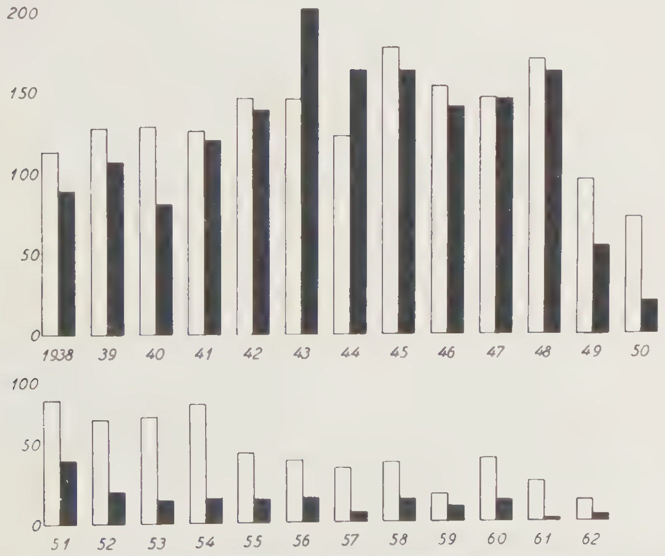

Figure 5. Annual number of newly notified cases of tuberculosis in Copenhagen per 100,000 in the years 1938–1962. City of Copenhagen Central Dispensary.

White columns: age-group 0– 8 years.

Black columns: age-group 9–14 years.

(Reproduced from Christensen, O., Danish National Association for the Fight against Tuberculosis.[4])

about 600. There are thus still many possibilities of contact with sources of infection. Because of the vaccination, we seldom see the small epidemics encountered, for instance, in Holland where mass vaccination against tuberculosis is not used. This applies to both school epidemics and outbreaks among soldiers and in other closed communities. The school epidemic which I mentioned earlier happened in 1943, before systematic vaccination of school children had been introduced.

The protection afforded by BCG vaccination against generalized tuberculosis must also be taken into consideration. For instance, in Copenhagen there was not one BCG-vaccinated person among the last 200 and more cases of tuberculous meningitis. In Greenland 20 years ago that disease was responsible for more than half of the deaths among children. It is now rarely encountered in this area and in none of the four fatal cases which occurred in the period 1956–1963 had the patient been vaccinated.

Another reason for continuing the BCG vaccination program in Denmark in spite of the low incidence of tuberculous infections in the population is the great increase in the numbers of both tourists and foreign workers.

THE EFFECT OF BCG VACCINATION ON INFECTION WITH M.AVIUM

It has been shown previously by Fenner[10] that BCG vaccination evokes heterologous immunity against infections with M. balnei and M. ulcerans. Studies on the effect of BCG vaccination on infection with M. avium have been carried out in rabbits by Engbæk and Jespersen,[9] and the results of one of their experiments are recorded in Figure 6. The ordinate shows the number of bacteria in the spleen of unvaccinated (open circles) and BCG-vaccinated animals (black circles) at different times after intravenous challenge with M. avium. As can be seen, the

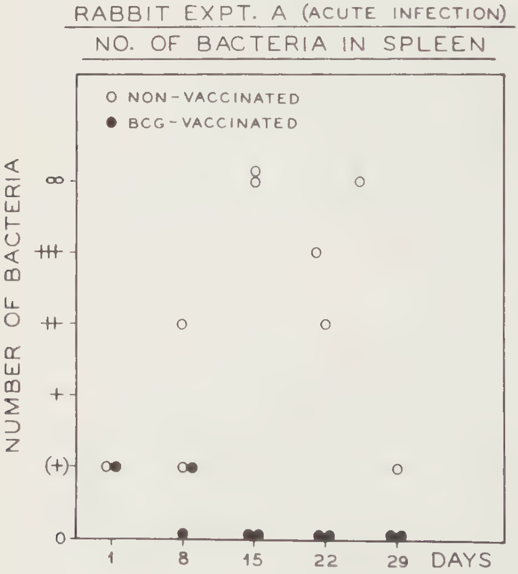

Figure 6. The effect of BCG vaccination on infection with M. avium. (Reproduced from Engbæk, H. C., and Jespersen, A., Acta path. scandinav.[9])

vaccination caused strong inhibition of the growth of bacteria in the organs. This is one of the most important changes in the reaction of animals with acquired resistance after BCG vaccination. Furthermore, the vaccination in rabbits changed an acute course of infection to a chronic one and prolonged the survival time. The vaccination also altered the course of disease in guinea pigs and mice.

On the basis of the present knowledge of the analogous effect of BCG vaccination in animals and humans, it seems justifiable to assume that the resistance acquired by means of BCG vaccination will also have an influence on humans as regards infections caused by M. avium and strains resembling M. avium.

SUMMARY

The prevention of tuberculosis by BCG vaccination is discussed on the basis of results obtained in mass vaccination campaigns and in populations with high infection risks. The protection afforded varies from very poor in some trials to extremely good in others. The possibility that the conflicting observations may be due to differences in potency of the various BCG substrains (used for the trials) is discussed and related to their behavior in experimental animals.

Results obtained by BCG vaccination in Denmark are presented, as well as the present status as regards incidence of tuberculosis and the program for continued control of that disease. Finally, some observations on the effect of BCG vaccination on infection with other mycobacteria are reported.

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The Common Cold: Prospects for Its Control

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A little more than 20 years ago the Medical Research Council established a common cold research unit at Salisbury. About that time or soon afterwards, a number of laboratories, in the United States and elsewhere, also began to study intensively the problem of colds. We now know a great deal about the viruses that cause colds and about their properties. However, after 20 years of work, colds are as common and as troublesome as ever. We may rejoice that typhus, plague, and yellow fever are no longer the menace they once were; but as far as our personal comfort is concerned, many of us would be more interested today in getting rid of the common cold. What are the prospects?

First, the agents involved: there seems little doubt that the most important agents concerned are the rhinoviruses, particularly as regards colds in adults. There are many serotypes, perhaps 80, forming a group within the large family of picornaviruses. These are named from pico—very small—and RNA, denoting their nucleic acid composition. They are among the smallest viruses, about 30 mμ in diameter; they lack a lipid-containing envelope, and therefore are stable in the presence of ether and chloroform, and they have an outer, fairly rigid, shell or capsule composed of a small number of subunits or capsomeres—the exact number of these is still in dispute. Rhinoviruses differ from enteroviruses and most other picornaviruses in being labile at pH 5. Unlike polio virus and other enteroviruses, they do not have to withstand the acidity of the gastric juice before reaching the cells in which they can multiply. Rhinoviruses grow in tissue culture at a lower temperature and pH than is customary; many, however, can be adapted to grow under more usual conditions.

As regards their requirements for growth, the rhinoviruses form a graded series. The first to be isolated, the D.C. strain, grew at ordinary temperatures, but was lost for some time soon after its original isolation.[2] Apparently at conventional temperatures it was fastidious about the properties of the embryo in which it would grow but later it was adapted to grow in human diploid cells.[11] There is also the virus known successively as JH, 2060, and Echo 28 and now called rhinovirus 1A. This, too, would grow at conventional temperatures and pH, though it does better when these are rather low. There are a number of so-called M strains, which can multiply in monkey as well as in human tissues and are generally more adaptable than the H strains, which are the most numerous of those studied. At first they could be grown only in human embryonic kidney. Later most could be adapted to human diploid lines and to some but not all lines of HeLa cells.

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Using suitable methods of cultivation particularly as regards temperature and pH, workers could now isolate from nasal washings of patients with colds numerous rhinoviruses or some other viruses I shall mention later. Yet this could be done successfully in only 25 per cent of the washings. Many washings would transmit colds to volunteers yet yield nothing in culture. The use of a modified organ-culture technique has changed this and recently Tyrrell and Bynoe[10] were successful in cultivating viruses from 25 out of 33 colds. Most of these were rhinoviruses that could be first isolated only in organ cultures, but could later be adapted to grow under the ordinary "rhinovirus" conditions. Some, which are apparently myxoviruses, came to light under similar circumstances. There seem to be some rhinoviruses that grow only in organ cultures because they insist on differentiated ciliated epithelium before they will multiply, yet do only limited damage to the ciliated epithelium. One such strain has been described,[7] but this one damages ciliated epithelium and stops ciliary action so promptly that observation of its cessation can be used as a criterion for titrating the virus or antibodies against it.

There are organisms other than rhinoviruses that can cause the symptoms of common colds: the parainfluenzas, especially types 1 and 3, the respiratory syncytial virus, influenza A and B, Coxsackie A21 and some echoviruses, adenoviruses, and Mycoplasma pneumoniae or Eaton agent. These viruses are mostly not exclusively common cold viruses, but cause colds as a side line to their ordinary pursuits. The parainfluenza viruses are better known for their role in causing febrile or afebrile respiratory infections in small children; these infections are often accompanied by croup or bronchiolitis. Infection with parainfluenza viruses does not always lead to permanent immunity; reinfections in adult life may present as common colds. The same is true of the respiratory syncytial virus. These and the other agents I have mentioned can cause a spectrum of respiratory disorders with pneumonia at one end and a common cold at the other. It is very important to learn how to produce effective vaccines against them, so that we may protect small children from serious or even fatal lower respiratory disease. Vaccination against adenoviruses is likely to be useful in special circumstances, as in aggregations of service recruits. If it proves practicable to make polyvalent vaccines incorporating many agents, the parainfluenza viruses and others may well be included. But their contribution by themselves to the mass of common colds is not sufficiently great to make it likely that defense against them will greatly diminish the incidence of colds in adults.

The possibilities for making effective rhinovirus vaccines are both good and bad: good, because it has been shown that a formalinized vaccine against a particular virus can be made and can be shown to be effective; bad, because of the multitude of serotypes to be protected against. Several workers have reported evidence that volunteers whose sera contain antibodies to a particular rhinovirus are relatively resistant to experimental inoculation with that virus. It has also been shown that parenteral injection of a live or formalin-killed rhinovirus vaccine will lead to a rise in level of specific antibodies.[5, 9] Indeed it would not be strange if such vaccination should actually produce better antibodies than those that follow a natural infection, which affects only superficial mucous membranes. Accordingly, it is not surprising that vaccines can afford specific protection against challenge with the strain used to make the vaccine.[1] Two rhinovirus types, A1 and A2 (formerly known as Echo 28 and B632), have much in common in their antigenic make-up, and vaccination with one has led to antibody rise against both. Probably challenge experiments would have revealed similar crossing. These two types are unusual, however. Most rhinoviruses appear to be highly specific, as judged by results of neutralization tests. There is no evidence to indicate that crossing revealed by complement fixation tests is, among these and other picornaviruses, of significance for protection.

What are the prospects of making a polyvalent vaccine effective against many rhinoviruses? So far, it has not been possible to dilute a rhinovirus vaccine very far without loss of potency. Tests now in progress may, however, show that a bivalent or trivalent vaccine can be made and still be effective. But a polyvalent vaccine with 80 components is likely to be a different matter. First, vaccines must be made against all these strains and they must be so potent that each can stand being diluted 80 times. Then it must be verified that the 80 antigens all concentrated together are not toxic, either locally or generally. There is also the factor that when the body is offered a number of antigens simultaneously, it does not react equally against them all but is apt to pick and choose in an apparently haphazard manner.

Are there ways around this difficulty? One thinks of influenza and its vagaries. Can it be that of the many rhinovirus serotypes only a few are prevalent at any one time and that a World Common Cold Center could collect information and advise which are likely to be troublesome at a particular time and place? Present evidence does not make this very likely. Some types have been locally and temporarily prevalent, it is true, but others have been sporadic in incidence.[6] Antigenic make-up of a rhinovirus may well change with time, as with influenza, but evidence about this is lacking. Although the viruses are highly specific by laboratory tests, is it possible that some immunization might be achieved by successive infection with several apparently unrelated types? This does happen with some diseases, yet epidemiologic evidence does not encourage us to hope that it will occur in the common cold field. Nasal stimulation by several different colds does not seem to ward off the next one. Nor do we acquire solid immunity after many decades of exposure to all sorts of strains. The relative freedom from colds of older people may well be explained by less frequent contact with cold sufferers, especially those highly effective spreaders of infection—children. Can we hope that chemical degradation of rhinovirus antigens will give us a product with a broad range of immunizing powers? This is worth looking into, and in addition the possible role of interferon must not be forgotten.

I shall say very little about the use of bacterial vaccines for preventing colds, for they have been tested over many years and much has been written on the subject. Most controlled trials have shown no convincing evidence of their value; yet many people go on believing in them and using them.

I may sound pessimistic, but there is a brighter side. Some people never get colds. Why? Some people go a whole year without a cold. Why? Many people go through a whole summer without a cold. Why? If we knew the answers we might decide that an attempt to find a vaccine is by no means the best approach.

We certainly need to understand more about the epidemiology of colds. There are two schools of thought concerning the fundamental matter of how colds spread and why they occur in waves when they do. Dr. Tyrrell, now in charge of the work at Salisbury, has been carrying out experiments on the spread of common cold viruses from person to person. He, with Dr. Bynoe and Dr. Buckland, found that virus that is shed comes mainly from the nose, and is most effective when contained in the medium-sized droplets that are trapped in the nose.[3] A fairly big dose is necessary to produce a cold, and sneezing and handkerchief blowing are especially effective in transmission. Emphasis is thus on person to person spread of a clinical cold. On the other hand, Dr. Hope-Simpson, a general practitioner in Gloucestershire, takes an opposite view.[8] He notes the rise and fall of incidence of colds at different times, observes a close relationship with temperature and relative humidity, and doubts whether person to person spread is of much importance since the facts of epidemiology are quite inconsistent with such a view. I am impressed by both sets of data and have tried to reconcile them.[1] It seems possible to me that Tyrrell's data concern the transmission of clinical colds only, and that virus in small subclinical quantities is being spread much more readily than might appear. Consequently many people may harbor rhinoviruses and perhaps other viruses in their noses, temporarily and harmlessly. We know, in fact, that rhinoviruses may be recovered from the noses of healthy people. Stresses such as sudden changes in weather may render carriers temporarily vulnerable. Many of them may thus have their viruses activated, and they may pass them on very freely to contacts, so that a wave of colds is apparent.

These different views present a problem. Should we try, by using aerosols or other methods, to stop cross transmission by sneezes, or should we seek to learn how to soften the impact of the stress that renders people temporarily vulnerable? Possible methods of attack on the problem are many and various. The field is wide open and merely awaits the arrival of some genius.

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Respiratory Disease and the Adenoviruses

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The adenoviruses are an ubiquitous group of agents found naturally in association with the upper respiratory and gastrointestinal tracts of man and higher vertebrates. They are multiply speciated and are differentiated one from another by serological methods; at least 45 immunologically distinct members are recognized in the group. Of these, 28 are recognized as of human origin. Certain of these viruses, particularly types 3, 4, and 7, have been associated with acute respiratory infections, both epidemic and sporadic in distribution. Type 8 virus appears to have been a major cause of epidemic keratoconjunctivitis. The remainder of the human viruses are recognized in association with human illness far less regularly; their precise role as causes of human infections remain to be determined.

In this communication the nature of human infection and disease caused by adenoviruses types 3, 4, and 7 will be considered; emphasis is placed upon the clinical and epidemiological aspects of naturally occurring infection. The observations which follow were made in populations of young adult males recently removed from civilian life to active military duty. They are representative of the acute respiratory disease (ARD) problem seen by military physicians, but do not accurately reflect the situation found in civilian life. They are presented as a clinical and epidemiological model of an acute respiratory infection occurring in young adult populations who, in large aggregates, are adapting to a striking change in their way of life.

THE ENVIRONMENT

This environment has been variously described in psychological writings,[5] and inferred by TV and movie directors in a more or less stereotyped manner. However, surprisingly few scientifically sound ecological evaluations have been made of it. The basic combat training base is more often than not the sprawling complex of barracks, classrooms, training fields, and gunnery ranges surrounded by land of little economic value that is generally described in novels or shown in films. Superficially it is this to the recruit as well, at least as he rides to the

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Reception Station for processing into service. However, it does not remain that way to him very long. After being given an issue of clothing, he takes a battery of aptitude tests, is oriented to the life he will lead during basic combat training (BCT), is given physical examinations, eye and dental inspections, and is multiply immunized, all within a three to seven-day interval. Finally, he is arbitrarily grouped with 50 to 65 of his fellow recruits and moved to a BCT company. Immediately, his horizon narrows to *his* barracks, *his* mess, *his* branch PX and, most important, *his* drill sergeant. He realizes that he is one of four or five such units in *his* company, but only vaguely recognizes that five or six other companies were formed with his, or that there are 10,000 to 12,000 men in BCT with him. In his new environment he instinctively recognizes the drill sergeant as the leader, but must learn to depend upon him for guidance towards successful completion of BCT, for proficiency in military science and techniques, for attention, respect, and recognition. The drill sergeant attempting to forge a solid group that works as a unit does so by time-honored military training methods. The unit is emphasized above the man; his identity must merge with that of the platoon. His individualness no longer exists, except in his name. He wears the same clothes, sleeps in a similar bunk, uses the same latrine, eats the common meal, is exposed to the same instruction, and, indeed, has the same cropped head as the man next to him. He must perform to an as yet ill-defined standard, and aside from that of the drill sergeant, he has no concrete example for performance. He works harder than he ever has previously, often in adverse weather, often for longer hours without the diversions he enjoyed as a civilian. It is in this microcosm that the recruit is infected and develops respiratory illness. What then happens to the man, and the men in his unit?

ARD, THE DISEASE

Between January and March, 1965, my colleagues, Drs. Robert E. Blount, Lloyd C. Olson, and John A. Stephenson, and I studied the sequence of infection and disease in recruits entering BCT at Fort Dix, New Jersey. From previous work at that post we knew that approximately 50 per cent of the men would develop ARD of viral etiology. Approximately half of these would present with disease severe enough to remove them from training duties for four or five days as hospitalized casualties; one to four of them would develop an interstitial pneumonia which would disable them for three to four weeks. We therefore chose 48 men as they arrived at the Reception Station and began our linear investigation that hour. Our aims, among others, were to assess the occurrence of ARD in the group, to document the spectrum of clinical manifestations, to classify the severity of disease, and to determine its etiology.

We identified our interests and the design of experiment to the group under study and explained to them their role in our clinical and laboratory investigations. We saw each man every day, usually between 4:00 and 7:00 P.M. At this time each man was questioned concerning illness or indisposition for the last 24 hours, was given a cursory examination of the nose and throat; his oral temperature was taken, and if it was over 37.5° C., a more complete examination was made in order to document precisely signs and symptoms of ARD. Twice each week the nasopharynx of each afebrile man was cultured for bacterial and viral pathogens. No treatment was given by our team; rather, individuals were seen as required by the unit's dispensary physician, who determined whether treatment, including hospitalization, was warranted, and effected it. Each hospital admission from the group was studied bacteriologically and virologically upon admission.

We knew at the outset that graded clinical evaluation would be difficult, for *all* recruits in BCT have cough, coryza, sneezing, sore throat, hoarseness, myalgia, malaise, burning eyes, and headache at one time or another. Most have dry mucous membranes and pharyngeal injection as a "normal" finding. This study group was no different, and we found that fever, its degree and duration were the only reliable objective indicators of disease. The criteria ultimately developed for classifying ARD in this group is summarized in Table 1. Patients with coryza, cough, sore throat, and/or hoarseness with oral temperatures of less than 37.5° C. were considered as afebrile ARD. Those with temperatures between 37.5° and 38.4° C. were considered to have mild febrile disease if they were febrile at least two days during a seven-day interval, and showed objective signs and symptoms of respiratory tract involvement. Severe febrile disease required a temperature of at least 38.5° C. on one day, and one greater than 38° C. on the next, along with objective evidence of upper respiratory infection (URI) on those days.

When these criteria were applied to the respiratory illnesses encountered in the study group, the pattern of disease summarized in Table 2 emerged. First, 92 episodes were observed over the eight-week interval; 51 were afebrile, 17 were considered to be mild febrile URI, and 24 were classified as severe febrile URI. The 92 episodes resulted in 24 hospitalizations; most but not all those hospitalized were from the severe febrile group. Thus 50 per cent of the total strength was hospitalized during BCT. Next, the incidence of disease rose abruptly in the first two weeks of the study to peak in the second and third weeks of BCT. This peak is also reflected in the hospital admissions. However, the distribution of afebrile URI by week of training differed from that of mild and severe febrile disease. Thirty-nine of 51 episodes of afebrile URI were observed before the third week of training, whereas mild and severe febrile illnesses were more common in the third week and later. This pattern of disease distribution in BCT is typical for basic combat trainees during winter months.

The etiologies of disease in this group are summarized in Table 3. Here implicated etiologic agents are listed for afebrile, mild and severe febrile disease for hospitalized and nonhospitalized illnesses. The

Table 1. *Criteria for Clinical Diagnosis of ARD*

Afebrile:	Temperature < 37.5° C. but symptomatic, or with objective findings of URI.
Mild febrile:	Temperature 37.5 to 38.4° C. on at least 2 days with concomitant objective evidence of upper respiratory infection (URI).
Severe febrile:	Temperature > 38.4° C. on one day and > 38.0° C. on a consecutive day with objective evidence of URI on those days.

Table 2. *Nature of ARD in Army Recruits: Incidence and Clinical Severity by Week of Basic Combat Training (BCT), January–February, 1965*

ILLNESS	NO. MEN/WEEK BCT									TOTAL
	0	1	2	3	4	5	6	7	8	
Total strength	48	48	48	48	46	41	40	39	39	
Afebrile URI	10	16	13	11	1	0	0	0	0	51
Mild febrile	0	6	3	3	2	1	0	1	1	17
Severe febrile	1	1	7	13	0	2	0	0	0	24
TOTAL	11	23	23	27	3	3	0	1	1	92
Admitted to hospital	0	3	7	11	0	2	0	1	0	24

URI, upper respiratory infection.

Table 3. *Disposition and Etiology of ARD in Army Recruits January–February, 1965*

DISPOSITION/ETIOLOGY	NO. MEN IN CLINICAL CATEGORY		
	Afebrile	Mild Febrile	Severe Febrile
Hospitalized			
Adenovirus 4		1	17
Rubella			1
Streptococcus, β-hem.		1	
Pneumococcus			1
Unknown		2	1
TOTAL		4	20
Not Hospitalized			
Adenovirus 3		1	
Adenovirus 4	15	6	2
Parainfluenza I			1
Unknown	36	6	1
TOTAL	51	13	4

significant observations summarized here are first, none of the 51 trainees with afebrile URI were hospitalized; this reflects the policy for hospitalization at Fort Dix, New Jersey, where in general only persons with febrile disease are admitted to hospital. The etiology of this afebrile disease is for the most part undetermined; thus no pathogen was associated with the disease in 36 of the 51 patients in this category. Adenovirus type 4 was associated with disease in the remaining 15 patients. On the other hand, the etiology of febrile URI, both mild and severe, was more commonly determined. Adenovirus type 4 accounted for disease in 18 of 24 hospital admissions and types 3 and 4 for 9 of 17 patients with febrile illness who were not hospitalized. Rubella and beta-hemolytic streptococci were responsible for hospitalization of one patient each, and D. pneumoniae was recovered from the sputum of a single patient hospitalized with lobar pneumonia. Among those not hospitalized, the only other agent implicated was parainfluenza virus, type 1. Thus, while adenoviruses were the most prominent cause of febrile disease, the etiology of an appreciable segment of afebrile disease remained undetermined.

These data illustrate another significant and heretofore undocumented fact that significant numbers of recruits with febrile disease do not become hospitalized casualties. Of the 41 patients with febrile illnesses, 17 were able to carry on with their training during the febrile episode. Only 4 of the 17 were considered to have severe febrile disease; nevertheless, study of the clinical records of these men revealed that their illness was remarkably similar to those in the same category who were hospitalized. They were febrile just as long (average 3.6 days compared to 3.5 days) and presented the same symptoms of severe cough, hoarseness, anorexia, headache, and myalgias. Further, they had the same reasons and opportunities to seek medical care but did not. At least two of these four were advised by our physicians to attend sick call. Both felt that they could continue basic training, and that this was more important than the symptomatic treatment that hospitalization would offer. All four patients were highly motivated in this respect, and historically indicated that in civilian life they seldom lost time in school or at work from illness. This is a point of interest, since it suggests that previous training and experience in the home may influence the way with which the diseased recruit himself manages his disability, and that motivation is the important facet of the antecedent cultural pattern that needs further study.

These observations illustrate the characteristic features of recruit ARD during the winter months. Attack rates for hospitalized disease approach 50 per cent of recruits during the eight-week interval; the majority of patients are febrile, and have associated infections with adenoviruses. Most afebrile disease does not lead to hospitalization, and its etiology is for the most part obscure. The inference that much of this disease is associated with rhinovirus and other enterovirus infection is supported by observations of Lennette at Fort Ord, California,[1] and ourselves in yet other studies at Fort Dix, New Jersey. While this is of epidemiological interest, the benign characteristics of the afebrile infections do not press as strongly as does the febrile hospitalized disease for solution.

CONTROL

Although ARD in recruits was recognized as a distinct epidemiological entity during World War II,[3] widespread efforts at control were not significantly effective until killed specific adenovirus vaccines became available in early 1958.[6] These early vaccines were bivalent (types 4 and 7), later in 1962 were trivalent (types 3, 4 and 7) and could be shown to reduce hospitalizations for type-specific disease in direct proportion to their antigenicity. This was variable from lot to lot and from one manufacturer to another, and during the five years of their use, variation in antigenic potency was considered a prime developmental problem. At best these vaccines effected a 70 per cent reduction in type-specific disease; at their worst, they had little effect upon ARD when administered early after arrival on post. The overall mean reduction in hospitalization for ARD was approximately 40 per cent. The killed-virus vaccine therefore was useful but not completely satisfactory.

In 1963, after genetic material from the oncogenic simian virus SV 40 was found to be incorporated within the envelope of the adenovirus vaccine seed stocks, the killed-virus vaccines were withdrawn from the market in this country. Recruit populations since have not had the benefit of immunization. However, during recent years, Dr. Robert Chanock of the National Institutes of Allergy and Infectious Disease, Bethesda, Maryland, developed and evaluated a living attenuated adenovirus type 4 vaccine for protection against that specific infection.[1] Preliminary experiments by him and his associates showed that volunteers could be inapparently infected upon ingestion of this attenuated virus, and that they were immune to subsequent challenge four to six weeks later. Dr. Chanock then moved to small, carefully controlled field trials of this vaccine in Marine recruits.[2] In 1964, with collaborating naval medical officers, Dr. Chanock demonstrated that administration of this vaccine to Marine recruits at the Parris Island depot, effectively reduced both hospitalization for ARD and adenovirus type 4 infections which ordinarily occur in epidemics when recruits are transferred to Camp Lejeune for advanced training. In this epidemiological situation, Marines could thus be effectively immunized at Parris Island two to four weeks prior to exposure to infection. These preliminary tests showed that when the vaccine virus was administered in an enteric-coated capsule to recruit volunteers, it produced a selective intestinal infection which was silent, noncommunicable, and highly effective in preventing type 4 adenovirus illness severe enough to require hospitalization. It remained to be shown that this immunization would be effective in those epidemiological circumstances in which recruits are exposed to natural adenovirus infection within seven to ten days of arrival for BCT. These circumstances exist at Fort Dix, New Jersey, where two separate vaccine evaluations were made.

With the concurrence of the Surgeon General of the Army, the Vaccine Evaluation Board, National Institute of Allergy and Infectious Diseases, National Institutes of Health, and the active collaboration of the Surgeon and Training Command, Fort Dix, New Jersey, this evaluation was commenced in early October, 1965, at a time when rates for hospitalization of recruits for ARD during eight weeks of BCT varied from 15 to 25/100. The vaccine virus used in these studies was an adenovirus type 4 (strain CL 68558) which was propagated in human diploid fibroblast cultures, and which was shown to be free of adventitious microbial agents and of oncogenic potential in newborn hamsters. The single preparation (Lot 4) was lyophilized, mixed with an inert vehicle, and prepared into enteric-coated capsules, each of which contained approximately 10^6 TCD_{50} of virus.

Originally proposed for eight companies of recruits, the study was reduced to six companies by administrative problems of recruit disposition. Men immediately entering the Reception Station, Fort Dix, from civilian life were alternately administered the vaccine or a placebo capsule as determined by the last digit of serial number (odd or even) in numbers adequate to insure the formation of a study company of 225 to 250 men. Vaccine or placebo was administered within four hours of arrival on post. Administrative processing of immunized personnel was responsible for the loss of approximately 15 per cent of the total; these men were either assigned to other companies on the post or were lost to levies of troops for training at other basic training centers. After units were formed in the company area, company rosters were checked against the original immunization rosters. Each company save one had, in addition to those receiving vaccine or placebo capsules, a small number of persons receiving neither. These were men assigned to companies after immunization rosters had been completed; while these persons were followed for respiratory disease during BCT, they were not included in the final comparisons.

Hospital admissions for ARD were monitored continuously following admission of a man to the study; daily, men admitted during the preceding 24 hours were examined by one of the study physicians, the clinical diagnosis of ARD confirmed, and clinical samples for recovery of respiratory viruses and serological confirmation of disease were obtained. Throat washings were obtained in Hanks balanced salt solution (BSS) containing 0.4 per cent bovine plasma albumin (BPA), and no antibiotics. After appropriate treatment, these were tested for respiratory viruses by inoculation of primary human embryonic kidney (HEK) and rhesus monkey kidney (MK) cell cultures. Patients were bled upon hospital admission and again 14 to 21 days later for confirmatory serologic tests.

The results of this field evaluation of vaccine effectiveness are summarized in Table 4. The number of patients and rates/100/8-week interval for hospitalized ARD and adenovirus type 4 disease are summarized for each of the six companies under study in the fifth and sixth vertical columns. ARD in both vaccinees and controls was considered associated with adenovirus type 4 if this virus could be recovered from

Table 4. *Occurrence of ARD and Adenovirus Type 4 Disease Vaccine Evaluation I, Fort Dix, Fall 1965*

UNIT	DATE (1965)		STATUS	NUMBER AND RATE (8 wks.)		PER CENT REDUCTION IN ARD	
	Immun.	BCT	(N)	Hosp. for ARD	Adenovirus Dis.	Hosp.	Adenovirus Dis.
2I	10/10	10/18	V(105)	5 (.05)	0 –	77.3	
			C(114)	24 (.22)	19 (.17)		
2L	10/18	10/25	V(94)	6 (.06)	2 (.02)	57.3	
			C(87)	12 (.14)	9 (.10)		
3E	10/18	10/25	V(112)	3 (.03)	0 –	71.3	
			C(125)	20 (.16)	19 (.15)		
3T	10/25	11/1	V(99)	8 (.08)	2 (.02)	72.4	
			C(121)	35 (.29)	35 (.29)		
2S	10/25	11/1	V(99)	13 (.13)	1 (.01)	45.8	
			C(86)	21 (.24)	17 (.20)		
2W	11/1	11/8	V(98)	5 (.05)	1 (.01)	76.2	
			C(105)	22 (.21)	17 (.16)		
	Totals		V(607)	40 (.069)	6 (.01)	67.1	95.5
			C(638)	134 (.210)	116 (.18)		

BCT, basic combat training.
N, numbers.
V, vaccinees.
C, controls.

pharyngeal washings of patients obtained within 24 hours of hospitalization, or if significant increases in CF or neutralizing antibody could be demonstrated during convalescence or both. Actually adenovirus type 4 was recovered from all but 20 of the 116 persons in the control group considered to have adenovirus disease. Among vaccinees the diagnosis was established by virus isolation and serologic confirmation in two of the six; the remaining four diagnoses were made by serology alone. In only three instances was adenovirus 4 recovered without obtaining serologic confirmation of disease. This occurred in a single vaccinee (Co 3T, sixth week BCT) and in two controls (Co 2W, sixth week BCT). Thus the type-specific disease rates indicated in the table are based upon diagnoses established by recovery of virus in the majority of instances.

From the table it can be seen that immunization effected a significant reduction in hospitalization for total ARD (67.1 per cent) and reduced adenovirus type 4 infections by 95.5 per cent. Because attack rates for ARD varied significantly between companies, the reduction in hospitalized ARD varied between 45.8 per cent and 77.3 per cent. Since so few adenovirus type 4 infections occurred among vaccinees, the extent of reduction of type-specific disease could be calculated only for the composite of six companies.

Encouraged by these results a second, more extensive trial was made at Fort Dix during the early months of 1966, in collaboration with Lt. Col. Thomas Lamson, MC, Fort Dix, and Dr. Harry M. Rose, Columbia University, New York. The vaccine employed in this investigation differed somewhat from that used in Evaluation I, and consisted of approximately 100,000 TCD_{50} (per dose) of adenovirus type 4 (strain CL 68558) mixed with an inert vehicle, compressed into tablets, and given an enteric coating. This preparation, with an appropriate placebo, was evaluated for effectiveness in suppression of ARD and type 4 adenovirus infections at Fort Dix, New Jersey, in the waning winter months, 1966, during an interval when attack rates for ARD in unimmunized personnel varied between 35 and 45/100/8 weeks.

The primary purpose of the investigation was to assess the effect that mass immunization, with subsequent continued vaccine administration, might have upon the occurrence and patterns of ARD in basic combat trainees. Accordingly, between February 3 and 6, 1966, 4537 trainees between the first and seventh week of training in the 3rd BCT Brigade, Fort Dix, were administered vaccine, and 4416 controls in the 2nd Brigade were given a placebo at essentially the same time. This included every trainee in each of 40 companies except those in hospital, in the stockade, or AWOL during the interval. After February 9, 1966, incoming trainees were given either vaccine or placebo immediately upon arrival upon the post, and formed into companies entering the 3rd Brigade (vaccinees) or 2nd Brigade (controls). Recruit inputs followed this schedule of "immunization" each week for 11 weeks through April 29, 1966. By that date 10,863 vaccinees (49 companies) and 10,397 controls (47 companies) had been admitted to the study. Hospitalizations for ARD from both brigades were monitored continuously from February 2 to date. Etiology of respiratory illness was sought using methods described earlier in a sample of men admitted each week from each company.

The influence that immunization had upon the occurrence of ARD in this study is summarized in Figure 1. Here the rates for hospitalized

ARD in the 2nd and 3rd BCT Brigades are plotted for each week between January 2 and June 29, 1966. The test interval (February 3 to April 29) is that during which each man in the 3rd Brigade was immunized. The data show that after reaching rates of 45 to 55/1000/week in January, they began to decline spontaneously in February and March in the unimmunized brigade. Introduction of adenovirus type 4 vaccine effected a more precipitous drop in ARD admissions (from the 3rd Brigade) and maintained these at a low level (12 to 16/1000/week) for approximately six weeks, after which they increased sharply to preimmunization levels. Rates in unimmunized personnel also increased but tended to lag approximately two weeks behind those in the immunized brigade. Thus after approximately six weeks of effective suppression the vaccine apparently failed.

The reasons for this apparent failure became obvious while it was happening. Whereas in early January the only detectable agent associated with ARD was adenovirus type 4, the agent associated with disease in the immunized brigade in early April was type 7 virus, and by the end of that month type 7 virus had replaced type 4 strains almost completely. During the same interval, type 4 virus was overwhelmingly more prevalent in the control brigade. During the late spring and early summer, after immunization was stopped, type 7 virus appeared in the second brigade and in late August was four to five times more common than type 4 virus in both brigades. Mass immunization in this setting

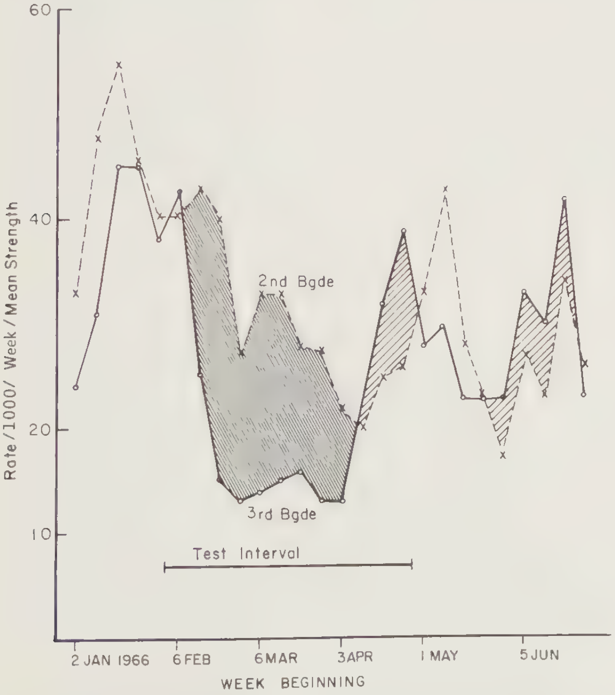

Figure 1. Occurrence of acute respiratory disease (ARD) among immunized (3rd Brigade) and nonimmunized (2nd Brigade) recruits, Fort Dix, N.J., 1966. (U.S. Army Photograph.)

therefore fostered the emergence of type 7 virus in a population which for the preceding six months was affected almost exclusively by type 4 virus. Even though the infecting virus was changed, the overall incidence of disease remained unchanged.

It is clear therefore that administration of a monovalent adenovirus type 4 vaccine of maximal homotypic effectiveness is not the final answer to the control of ARD in recruits, since the emergence of another agent to fill the vacuum caused by suppression of a single pathogen likely will occur again. The prospects for control appear only discouraging if one looks solely to the successive, successful development of one virus vaccine after another; this approach is fraught with enormous technical and administrative difficulties, and years are often required to develop a vaccine from bench to application. On the other hand, those of us concerned with the problem look conceptually to other ideas for control. Adenovirus infection rates among susceptible recruits approach 100 per cent during eight weeks of BCT, even though only half are *overtly* infected. Why is it that only half those infected become ill? If the reasons for this difference were understood, it might be possible to modify the severity of the illness resulting from infection, or perhaps to suppress it entirely. It seems appropriate therefore to suggest more extensive study of host response to infection, looking not only at the respiratory tract and its disease-altered function, but also at host physiology as a whole. If it were possible to modify the host's response, regularly suppressing overt disease, it might then be feasible to improve upon nature's methods for infection, and the concept of immunization by controlled infection could be put to test. These approaches are, at the moment, theoretical and untried, but in pursuing the questions lies the work yet remaining to be done.

Finally, it is clear that this work is beyond the capability of any single investigator or his group. This task, along with others in infectious disease control, will require the coordinated efforts of tens, perhaps hundreds of investigators, who, in short supply in this country, can only be effective in this type of investigation by truly unselfish scientific collaboration.

SUMMARY

Acute upper respiratory infections caused by adenoviruses are by far the most significant cause of morbidity in military populations recently removed from civilian life. During winter months, adenovirus infection rates approach 100 per cent of susceptible recruits during 8 weeks of basic combat training. The disease is of variable clinical severity, but results in hospitalization of approximately half those infected. Both infection and disease caused by adenovirus type 4 can be effectively suppressed by administration of a living attenuated adenovirus type 4 vaccine. In one extensive field trial, however, suppression of type 4 virus fostered the emergence of type 7 virus in the immunized population. Type 7 virus, once introduced, ultimately replaced type 4 virus as the epidemic strain, and the ultimate result was no significant reduction in acute respiratory infections.

ACKNOWLEDGMENTS

The original observations recorded in this manuscript obviously result from the efforts of many persons. Special recognition is given to the officers and en-listed men of the Department of Virus Diseases, Walter Reed Army Institute of Research, for their professional and technical efforts, to Col. Clyde Baden, Inf., of the Training Command, Lt. Col. Thomas Lamson, MC, and Capt. Clyde Locke, MC, of the Office of Preventive Medicine, Fort Dix, New Jersey. Harry M. Rose, M.D., College of Physicians and Surgeons, Columbia University, was the prime collaborator for investigation of the etiology of acute respiratory disease in the second large adenovirus vaccine field trial at Fort Dix, 1966.

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Epidemic Influenza: Immunization and Control

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The problems confronting influenza control are clearly presented in the recurrent epidemics, the high incidence of disease in the affected populations, the age distribution of illness, and the differing case fatality among segments of the population. There is, further, the dislocation of community life and functions which may occur under the stress of rapidly mounting illness. In the absence of prompt therapeutic specifics, control measures are, perforce, directed toward prevention. Moreover, it is highly desirable that prevention should be the objective rather than the dismaying outlook of awaiting the assault of extensive illness upon the community and its medical resources with only a reparative hope.

Isolation and quarantine have not been feasible procedures in limiting the spread of influenza with its brief incubation period. The high mobility of present-day living and the inability to avoid crowds tend to reduce their plausibility. Nevertheless, circumstances exist under which such effort can be considered for protection of the patient from added infection and of older persons from association with young dispensers of respiratory disease. Other efforts to sterilize limited environments of special groups have not been readily adaptable to general control procedures. Inevitably, attention has concentrated on immunological efforts toward control.

CONCEPTS OF IMMUNITY TO INFLUENZA

In times past many observers insisted that an attack of influenza conferred no immunity to clinical disease. This anomaly was of itself a forewarning of the antigenic multiplicity of the etiologic agent. At present there are numerous shades of opinion, frequently unsubstantiated, as to the degree, the duration, or the basis of resistance to the disease. On the other hand, there are firm reasons to consider immunity to influenza in accord with classical immunology, reinforced by increased knowledge of the agent, the host, and the pathogenic mechanisms.

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The age distribution of epidemic influenza has consistently expressed the comparative resistance of different age groups. The major prevalence of clinical disease is commonly in the ages of 5 to 14 years, with levels which may reach 50 per cent or more, well in excess of that of the total population. After 40 years of age, there is usually a distinct or progressive decrease in incidence. In contrast, it has been noted repeatedly that when epidemics of the same virus family recur in the same region at short intervals after a pandemic spread, the incidence under 20 years may be proportionately reduced, strongly indicating an effective and acquired sustained immunity. Further, in many of these recurrences of the same virus family different persons are affected, but this is not always so in children. Studies in our laboratory, well substantiated by others, have demonstrated that these first experiences leave a lasting immunological imprint upon that population cohort, which is repeatedly enhanced by subsequent exposures so as to characterize the group throughout life by the nature of its first viral experience.[8, 9, 20] In addition, the subsequent exposures induce further antibody to respective strains, so that the older segments of the population possess a broad range of antibody to multiple antigens of related strains. It is postulated, then, that the reduced incidence in older persons is related to the accumulated composite antibody. Moreover, there is good evidence that the cross-reacting antibody so induced is of high avidity and specifically orientated.[6]

Epidemiologic studies have shown conclusively that there is a distinct relation between circulating antibody levels to the current virus and resistance to natural infection, although individual exceptions may be noted. Antibody produced by infection (or vaccination), however, is not necessarily strain-specific, since even young children, by virtue of cross-relationships among the respective strains, during convalescence from a given infection may develop antibody which reacts with temporally remote strains which they would not have encountered directly. In many instances human adults or experimental animals infected with a strain of one family of influenza A virus will show wide antibody coverage against most strains of that family and increased antibody against others as well. Influenza viruses of a given type are then conceived to be composed of a number of common antigens which may be expressed to different degrees in the various strains and families of that type. The antigenic variation is thus thought of as a rearrangement of constituents rather than complete loss or gain de novo.[18, 29]

Influenza virus exerts its primary injury on the ciliated epithelium of the respiratory tract.[15, 21, 27] Since this tissue is essentially extravascular, virus can theoretically alight thereon without being encountered by circulating antibody. In fact, after recovery from a primary infection with a well adapted strain, the restored epithelium may again be damaged by instilled virus, apparently escaping neutralizing antibody of the blood.[15, 21] Interestingly, these animals do not develop the extensive pneumonia seen in controls. Twenty-five years ago, in an effort to understand how circulating antibody participates in protection, we studied the nasal secretions. Antibody could be demonstrated in them, paralleling to a degree that of the blood; it was increased after infection or vaccination. It was concluded that at the primary level the antibody at the portal of entry, the nose, was a significant feature in protection.[15, 16]

At one time, alterations in the susceptibility of the respiratory epithelium seemed a possible factor in accumulated resistance, since rests of modified, unaffected cells were seen in reinfected animals.[11] The possibility that such changes may participate in the resistance of older, experienced persons should not be dismissed. Similarly, alterations induced in the permeability of the respiratory tract by chronic pulmonary or cardiac disease, or pregnancy, with chronic hyperplasia of the alveolar cells, may affect the availability of antibody at the portal, and unfavorably influence the behavior of older and affected persons to infection.[26, 27] One can readily visualize as well that a mild focal damage to limited areas of the epithelium – as from experimental infection with strains of low virulence and small dose – leaves other unaffected cells which can be attacked in subsequent exposures, as with experimental challenge.

IMMUNIZATION WITH INFLUENZA VIRUS VACCINES

Control efforts have concentrated largely on prophylactic vaccination. The data accumulated from well-conducted studies have established beyond doubt the high effectiveness of appropriate inactivated vaccines against epidemic influenza. Much of the evidence derives from well-controlled studies in the high-risk group of military recruits where close observation could be maintained both clinically and by laboratory procedures. The first of these, conducted by the Commission on Influenza, Armed Forces Epidemiological Board, in 1943 with formalin-inactivated A and B viruses from chick allantoic fluid, demonstrated that subcutaneous vaccination had an overall effectiveness of more than 75 per cent during a sharp epidemic of influenza A. The same vaccines in 1945 had over 90 per cent effectiveness against epidemic influenza B. It must be emphasized that 75 per cent means a ratio of 4 in controls to 1 in the vaccinated, and 90 per cent represents a 10:1 ratio, therefore these are not minor effects. The significance of a major epidemic variant was demonstrated in a controlled study when the same vaccine had no protective effect against the newly-arrived A-prime virus (1947). The vaccine stimulated good antibody to the constituent strains, but not to the epidemic strain, although the natural disease stimulated antibody to both. Subsequently, the vaccines have comprised different strain combinations with consistent evidence of high effectiveness. In each situation effort has been made to gain additional information to guide vaccine formulation. The 1957 experience provided further evidence regarding the importance of antigenic dose. Vaccine containing only 200 CCA units was 50 to 60 per cent effective; 400 CCA was 67 per cent effective, and 750 CCA vaccine was 75 to 80 per cent effective.[38] At the Great Lakes Naval Training Station 83 to 90 per cent effectiveness was noted with the homologous vaccine, and suggestive effects (43 per cent) were noted after a swine, A-prime vaccine. These data have been summarized recently.[3]

This brings up another point requiring better understanding. That variability in influenza viruses is extensive has been recognized since the first serological differentiations among them were demonstrated. The differentiation of influenza A viruses into four epidemiologic and antigenic families, each comprising lesser variants, has been a later development. The strains of a given family or group tend to override

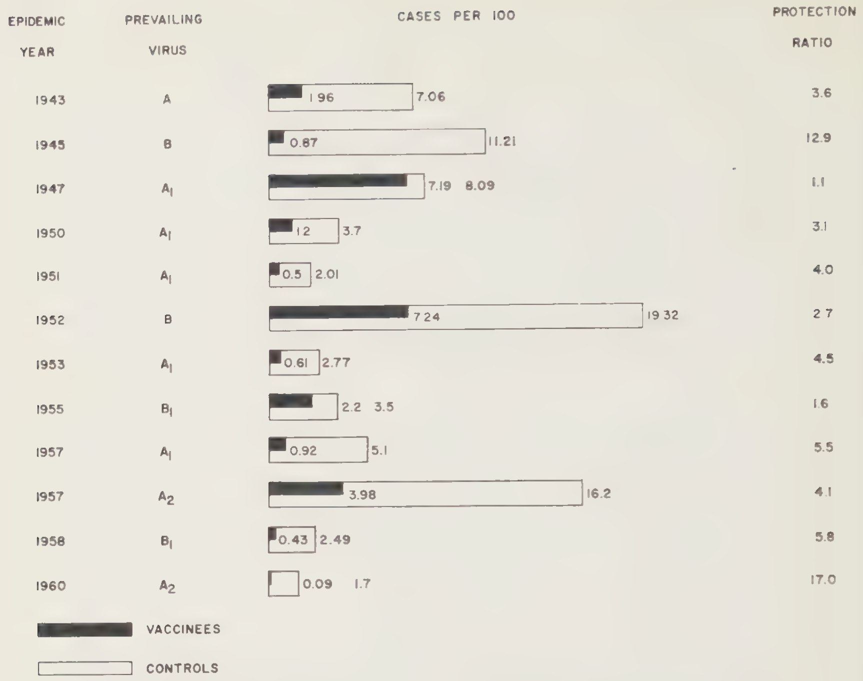

Figure 1. Results of vaccine field trials (Commission on Influenza).

the relatively specific immunity elicited by another, resulting in high incidence in young people; and yet, as mentioned earlier, the segments of the population above 40 years of age are comparatively resistant to apparently new major variants. Furthermore, experimental animals can by repeated injections of a strain of one family be immunized against those of another group, even though major quotas of cross-antibody are not observed.[17] Serum taken late after a primary inoculation, or after hyperimmunization, tends to show much more of the relationships than that taken shortly after inoculation of a limited dose. There are reasons to believe also that a strain maintained in egg or tissue culture presents a less fulsome display of antigenic components than when adapted to mice or ferrets.[30] These factors of themselves can influence the serologic measurement of antigenic relationships that are so derived. This information is important, as it concerns antigenic variations within the family and the urge to shift components in vaccine because of some demonstrable serologic differences among them. Despite the serologic finery which embroiders this area, the bulk of evidence supports the general conclusion that the antigenic similarities of strains within the family are sufficient to outweigh the differences observed; this applies to differences which may be noted among strains of the same family in the same epidemic. Robinson has suggested that infection studies in human volunteers might be helpful in clarifying the picture.[37]

The 1943 vaccine contained the PR8 strain of 1934 which Hirst insisted was the essential protective component; Meiklejohn reported a mild influence of a PR8 vaccine in an A-prime epidemic (1952). In 1945 and 1952 the Lee strain of 1940 was highly effective, but in 1955 when tested against a distinctive variant or subgroup, it was not. Addition of the 1954 B strain provided a vaccine that was over 80 per cent protective in 1959. The vaccine tested in the early 1957 A-prime epidemic induced poor HI antibody response to the epidemic strain, but protection above 80 per cent to the disease was observed.[32] British investigators reported that vaccination with a 1947 A-prime strain was as effective in 1956 as a 1955 strain of that group.[2] Well observed studies have indicated very good results against Asian strains in 1963 with vaccine containing the 1957 A_2 strain.[34, 35] The very low frequency of influenza among the American military forces in recent years seems certainly attributable to continued vaccination with A_2 strain. There is, therefore, field evidence that vaccination with strains of the same family isolated in different years can provide effective vaccines against their familial relatives; that the effect is not especially related to the time at which they were prevalent but rather to group similarity.

The foregoing evidence is not intended to indicate that the situation, good as it is, is completely satisfactory. Single doses of aqueous vaccine of reasonable potency are not uniformly effective among children in stimulating antibody to strains which they have not previously encountered. The applicability of larger doses of whole virus vaccine is limited by the low tolerance and the proportionately high frequency of local and febrile reactions in children, even though they may be readily counteracted by small amounts of acetylsalicylic acid. Two doses or more have, therefore, been recommended in these groups. It should be mentioned that the rumored accounts of frequency of reactions generally are not substantiated by close observations. The amounts of vaccine produced have not been sufficient to permit general use, and there are those who do not consider it advisable annually. The duration of effectiveness has not been adequately established on a clinical basis, although antibody levels may remain well elevated for considerable periods.

Mineral Oil Adjuvant Vaccines

In the effort to alleviate some of the mentioned difficulties and to enhance the effectiveness of influenza vaccines, considerable attention has been given to the use of adjuvant preparations of water-in-oil emulsions. The studies since 1952 have repeatedly emphasized that higher and longer antibody levels can be induced in man; materials collected by Bell showed persistence of high levels of antibody induced by monovalent adjuvant vaccines for at least eight to nine years in the absence of intercurrent boosters.[4] As little as 50 CCA units, or even 10 CCA units, of multiple strains in the same preparation have been capable in two doses, eight weeks apart, of stimulating antibody levels far in excess of those observed after aqueous vaccine, and they persisted for extended periods.

Adjuvant vaccine in primary inoculation establishes an active immunological base for boosting with aqueous vaccine or further adjuvant vaccine; it also serves as an excellent booster for the low levels achieved after the initial primary stimulation experience to a strain in an aqueous vaccine.[25] This effect appears in both children and adults and might be valuable in preparing the population immunologically for the advent or recurrence of major variants. Since less antigen is required, the number of doses of vaccine from the same amount of virus would be enormously increased and price would not be exaggerated. The breadth of antibody response could also be enhanced. It has been shown in mice that the antibody induced by such adjuvant preparations increases in the early stages with γM antibody similar to that after aqueous; but the γG began earlier and extended longer and to higher levels than seen after aqueous.[1] Hence, the type of antibody which persists at high level after adjuvant vaccines is of the highly protective variety.

Adjuvant vaccines have been administered with controls in several large field studies in military populations in the U.S.A.[3] Results have been of high order with 85 to 95 per cent protection against Type A strains. There is less information about influenza B, although limited observations indicate as high as 80 per cent effectiveness.[36] It should be noted that, in the military studies involving thousands of men, no cystic reactions have been encountered, except after the first preparation, and careful review has yielded no indication of carcinogenic effect. In fact, this is an obstructive deterrent unsupported by long knowledge of oils of the defined character. Reactions to whole virus vaccines are also largely avoided.

Briefly, it is difficult to understand why these materials have not yet been approved for general use by official agencies, since they withhold materials which have many advantages for the immunization of man. Multiple vaccines in addition to influenza could be combined in small amounts for a broad base of immunity to a number of agents, rather than the numerous individual preparations now employed. With a combined influenza virus and adenovirus adjuvant vaccine, Meiklejohn observed almost complete prevention of infection and disease from both causes in the same population in the same year.[33] It is recognized that the applicability to antigens of varied character must be determined.

Vaccination with Purified Antigens

A second line toward improvement of vaccines comes in the effort to obtain the essential antigens in purified form from the virus particle. This represents a most engaging outlook for preventive immunization. The work of Davenport, Hennessy, and their associates has demonstrated that purified HA of influenza virus obtained by ether splitting and precipitation of soluble antigen by lanthanum acetate induces antibody against intact virus in man and animals at least equal to that obtained with whole inactivated virus.[5, 24] In children and infants one to two years of age the febrile reaction is essentially eliminated, even when much larger doses of purified HA were used than could be tolerated in the form of virus particles. Younger infants of 9 to 29 weeks of age tolerated large amounts of HA vaccine well, and two doses induced significant antibody levels.[22] Thus, considerably more immunizing antigen can be used while eliminating the problem of reactions. Furthermore, the procedure releases largely concealed antigens to other strains, so that the material represents a pool of homologous and heterologous strain antigens in amounts than can be quantitatively measured by photometric methods and by cross reactions measured serologically.[7] In fact, because of antigen particle size, serological titers are commonly considerably higher when measured with HA than with intact virus. Preparations of the purified HA antigen have been prepared commercially without difficulty and have been used under field conditions, although mostly antigenic data have been obtained.

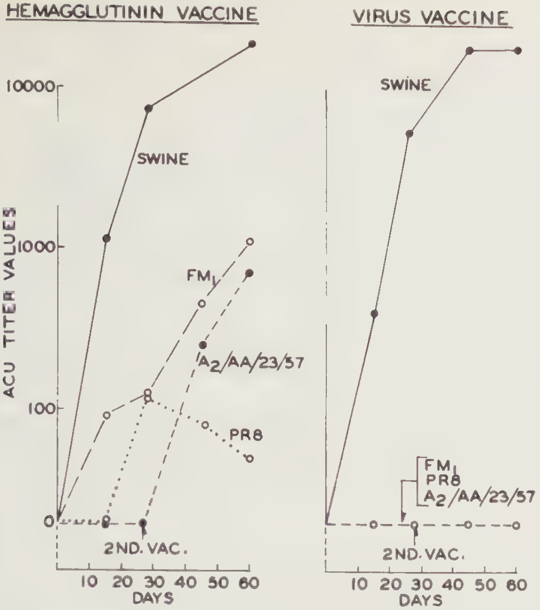

Figure 2. Antibody response of guinea pigs vaccinated with swine virus or with swine hemagglutinin.

This line of study has been pursued further with other materials used for viral disruption. Hobson,[28] using deoxycholate, prepared non-hemagglutinating material which possessed, however, the capacity to block the HI antibody of the homologous strain. The material did, moreover, induce antibody to other virus strains and families in guinea pigs. Eckert found,[10] using methanol-chloroform for lipid extraction, that the denatured protein residue was serologically inactive; when solubilized with acetic acid and then freed of acid, a heterogeneous protein was recovered which comprised aggregation of smaller 4s units and had HA properties, induced antibodies to intact virus, and reacted in CF with antiviral serum. Later, it was found that 8M urea with a reducing agent yielded a comparatively stable 4s component, which did not give HA but was active antigenically in rabbits, reacted in CF with antiserum and functioned as blocking antigen in HI. These components are thought to be envelope protein and may well be valuable products for further vaccine improvement.[11]

It should be emphasized in passing that evidence is steadily increasing at the biochemical or molecular level to support the immunologic evidence of multiple common antigens in various strains; that they are truly functional, as shown by Kilbourne et al.,[31] with recombinants, and that they can induce multiple antibodies in the same globulin molecule.[13]

SPECIAL EMPHASIS ON CONTROL

Attention to the vaccination of children is of prime importance if vaccine is to be generally effective, since they constitute the largest segment of the population and also display the highest morbidity. They are the most ready recipients of infection and also the most effective dispensers. It is noted that the incidence among adults is highest in families with children of 15 years or less, while adults in households without children have a sharply reduced frequency of influenza.[23] Grandparent baby-sitters should beware. Accordingly, the efforts to obtain vaccines of greater potency and broader coverage, laying a base for greater resistance to recurrent strains, are particularly relevant to the childhood problem.

On the other hand is the recognition that, although the older age groups have generally the lowest incidence of influenza, the case fatality is usually highest in them. It is here that mortality requires special consideration. The excess mortality accompanying the 1957 influenza in U.S.A. was about 10 per cent but 83 per cent of the deaths occurred in persons over age 45; 30 per cent of the excess was attributed to influenza and pneumonia, and nearly half to cardiovascular renal disease.[12] In 1958 and 1960 when the morbidity was reduced in the young, more than 90 per cent of the total excess deaths occurred in persons over 44 years of age. Britain had similar data, and in both countries the mortality from cardiovascular disease in subsequent years was less than expected.[19] It is my impression that much of this effect relates to reduced physiological competence in the elderly and that pathophysiologic factors such as potential decompensation in the face of acute injury to the cardiorespiratory system are the deciding influences. They may alter the effectiveness of antibody as well. This is seen further in the excess mortality in the presence of mitral stenosis particularly, and in late pregnancy. The ability to concentrate attention on these groups with vaccines of heightened potency and acceptability might well be decisive in tipping the balance in favor of resistance and survival.

It is clear that research and development are far ahead of application. The reasons for this I shall not discuss except to say that there is an excess of administrative reluctance, of ready opinion inadequately supported, and of a tendency to consider the well-founded data of effectiveness less important than flimsy arguments to the contrary. There is need for strong pressure to increase the use of potent and effective vaccine throughout the population. I have not mentioned live vaccine, because up to now the problems surrounding its wide use have been greater than those involving the inactive material. Nevertheless, as an emergency measure, it still should be considered.

Similarly, the continuing hopeful search for drugs which may be of prophylactic value has yielded sufficient indications in vitro and to some extent in vivo to make it an important line of study. Recently, certain products have been reported in a variety of studies to have a measurable prophylactic benefit in man. It has given increased impetus to the search which could, of course, yield valuable aids to control. Even then, however, however, the immunologic procedures would have numerous advantages in producing durable effects.

The desire to control influenza has roots in a long history of numerous and severe experiences. The materials now available make prevention possible well beyond the results attained. There is need to support the evidence of protective vaccination with added efforts toward application, rather than to be diverted from the attainable goal by captious restraints.

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Role of Mycoplasmas in Human Respiratory Disease

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Until recently the role of mycoplasmas in human disease was unclear. Within the past four years the observation that the Eaton agent is a mycoplasma and that this agent is the cause of cold agglutinin-positive primary atypical pneumonia[5] has been confirmed by a number of workers.[1, 2, 24, 27, 28, 31, 32]

This organism is serologically and biologically distinct from all other known human and animal mycoplasmas and has been given the name Mycoplasma pneumoniae to connote its relationship to pneumonia.[6]

Recently developed diagnostic procedures have made it possible to delineate the epidemiology of M. pneumoniae infection. The accumulated evidence suggests that it is a major cause of upper and lower respiratory tract disease. In addition, other mycoplasmas have been recovered from patients with respiratory disease, and the etiologic role of these mycoplasmas is being studied. A summary of our present understanding of mycoplasma-induced respiratory disease and a discussion of current concepts of prevention and immunization form the basis of this report.

MYCOPLASMA SPECIES OF MAN

Six serologically distinct species of mycoplasmas (M. hominis, type 1, M. salivarium, M. orale types 1 and 2, M. fermentans, and M. pneumoniae) and a group of biologically similar but serologically heterogenous mycoplasmas (the "T-strains") have been recovered from man (Table 1).[18, 20, 48, 53, 55, 66, 67]

In addition, another serologically distinct mycoplasma was recently isolated from the oropharynx of 1 per cent of ill or well adults studied.[23] This previously undescribed mycoplasma tentatively has been named Mycoplasma oral type 3.

Evidence associating M. hominis type 1 with human respiratory

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Table 1. *Mycoplasma Species of Man*

MYCOPLASMA	NO. OF SEROTYPES	SITE OF RECOVERY	ASSOCIATION WITH ILLNESS
M. hominis type 1	Multiple: related but distinguishable	Genitourinary tract (common) Oropharynx (uncommon) Pleural fluid, blood (rare) Products of abortion (rare)	Pelvic inflammatory disease (not definite) Pharyngitis, pneumonia (not definite) Septicemia (not definite)
M. salivarium	1	Oropharynx (common)	None
M. orale type 1 (M. pharyngis)	1	Oropharynx (common) Bone marrow (rare)	Isolated from bone marrows of leukemic children (rare)
M. orale type 2	1	Oropharynx (rare)	None
M. orale type 3*	1	Oropharynx (rare)	None
M. fermentans	1	Genitourinary tract (uncommon)	Inflammatory disease of the genitourinary tract (not definite)
M. pneumoniae	1	Oropharynx (uncommon except when associated with illness) Middle ear (rare)	Upper and lower respiratory tract disease (common) Myringitis (rare) Various cutaneous, neurologic conditions (not definite)
"T-strains"	Multiple: unrelated	Genitourinary tract (common) Oropharynx (uncommon)	Urethritis (not definite)

*New species.

disease has been obtained[44, 45, 68] but thus far only M. pneumoniae has been proved to be pathogenic for man. The "T-strain" group of mycoplasmas has been associated with nongonococcal urethritis, but an etiologic relationship remains to be established.[44, 21, 55] The role of "T-strain" mycoplasmas in human respiratory disease has not been evaluated.

M. hominis Type 1

M. hominis type 1 is the mycoplasma most commonly isolated from the genitourinary tract. In addition, it has been isolated infrequently from the blood, fallopian tube, or ovary of patients with pelvic inflammatory disease, septicemia, or postpartum fever.[64, 65, 72] Although serologic confirmation of infection was obtained in several of these patients, controlled epidemiologic studies are needed to confirm an etiologic role of M. hominis type 1 in such disease.

M. hominis type 1 has been isolated less frequently from the oropharynx than from the genitourinary tract. In a two-year study of hospitalized pneumonia patients, M. hominis type 1 was isolated more frequently from the pneumonia patients than from hospitalized controls with nonrespiratory disease.[44] When an isolate of M. hominis type 1 from one such pneumonia patient was administered to volunteers, a mild exudative pharyngitis-like syndrome was observed in a significant proportion of the men. Furthermore, clinical illness occurred more frequently in men who lacked preexisting antibody to M. hominis type 1, and infection was followed by a serologic response to the infecting organism.[45, 68]

The role of M. hominis type 1 in naturally acquired exudative pharyngitis is less clear. In a study of paired sera from 150 children with exudative pharyngitis and a comparable number of matched controls, only one patient with exudative pharyngitis demonstrated a rise in growth-inhibiting antibodies to M. hominis type 1.[52]

Other epidemiologic studies of respiratory disease have failed to demonstrate a relationship between M. hominis type 1 and exudative pharyngitis.[16, 26] Thus, M. hominis type 1 appears to be, at most, an uncommon cause of respiratory disease.

M. pneumoniae

At present M. pneumoniae is the only mycoplasma clearly pathogenic for man. Early studies that led to the description of cold agglutinin-positive primary atypical pneumonia as a new syndrome and that established its relationship to M. pneumoniae have been reviewed in detail elsewhere.[3, 22, 29] More recent studies have attempted to define the ecology of M. pneumoniae and its spectrum of illness.

M. PNEUMONIAE INFECTIONS

Ecology of M. pneumoniae

All degrees of respiratory involvement, from inapparent infection to pneumonia, occur following infection with M. pneumoniae. In two studies only 3 to 10 per cent of infections were estimated to result in clinically apparent pneumonia;[10, 12, 54] in another study 82 per cent of infected persons were found to exhibit some evidence of lower respiratory tract involvement.[24] Myringitis, often bullous, has been observed in artificially infected volunteers[12, 54] and following a small proportion of naturally acquired infections.[24, 59]

Infection with M. pneumoniae occurs throughout the year but is somewhat more prevalent during the fall and winter. True epidemics have been reported only in relatively closed military or institutional settings. This lack of epidemicity is consistent with the slow person-to-person spread and long incubation period characteristic of the agent. In a seven year study of pneumonia among Marine recruits, 38 per cent of all pneumonias could be attributed to infection with M. pneumoniae. The annual incidence of M. pneumoniae-positive pneumonias was 18 per 1000 persons in this population.[7]

There is now ample evidence that M. pneumoniae is an important cause of lower respiratory tract disease in civilian as well as military populations (Table 2). Thus, in studies in the United States, Great Britain, Finland, The Netherlands, and Sweden, M. pneumoniae was responsible for 10 to 33 per cent of all pneumonias. The annual incidence of pneumonia caused by M. pneumoniae in one large civilian population was estimated to be 1.5 per 1000 persons.[1]

Illness caused by M. pneumoniae is predominantly a disease of older children and young adults, although it may occur at any age (Table 3).[2, 28, 29, 32, 44] Moreover, in family outbreaks severe illness occurs more frequently in adults than in children under five years of age, who commonly experience asymptomatic infection. Family outbreaks are often quite protracted and introduction of the organism into the household occurs more often among families with school-age children. The secondary infection rate in such families is often high. Thus, 39 per cent of 151 family contacts of M. pneumoniae-positive pneumonia cases in 36 families demonstrated evidence of infection.[24] Surveys of antibody to M. pneumoniae in sera from persons of all ages suggests that children under five years of age are seldom infected.[70]

In a recent study of pneumonias the incidence of M. pneumoniae pneumonia was slightly higher in males than females, particularly in the younger age groups.[1, 28]

Wide fluctuations occur from year to year in the incidence of M. pneumoniae-associated disease in certain civilian and military populations.[5, 10, 11, 29] In contrast, the incidence of M. pneumoniae infection in other populations has remained relatively unchanged over several years.[1] The reasons for such differences are unknown.

The incubation period of M. pneumoniae illness as determined by studies of family outbreaks is approximately three weeks.[24] A shorter interval (ten days) was observed in volunteer studies.[35, 52, 56] However, the inoculum in some of the volunteer studies contained approximately one million organisms, and this magnitude of infection may have shortened the incubation period.

Prior infection with M. pneumoniae provides protection against severe illness but only relative immunity to reinfection. Thus, 17 of 22 volunteers with no demonstrable growth-inhibiting antibody to M. pneumoniae developed respiratory tract illness when challenged with this organism, whereas only 5 of 23 seropositive men became ill. All 45 men were infected as determined by isolation of the organism and a serologic response.[56] Similarly, a reinfection rate of 23 per cent was observed among seropositive Marine recruits who were exposed to M. pneumoniae during training. Infection occurred approximately three times more frequently among seronegative recruits in the same population.[7]

Clinical Characteristics

The pattern of disease observed following infection with M. pneumoniae is too variable to permit clinical diagnosis of individual illnesses.

Table 2. *Importance of M. pneumoniae in Lower Respiratory Tract Disease in Different Localities*

POPULATION	RESPIRATORY DISEASE	LOCATION	TIME	METHOD OF DIAGNOSIS	NO. TESTED	% POSITIVE	REFERENCE
Civilian							
College students	Lower tract	Wisconsin	1953–1960	Fluorescent antibody	119	22	19
Infants, children	Lower tract	District of Columbia	1957–1959	Fluorescent antibody	152	10	5
All ages	Lower tract	Great Britain	1962	Complement fixation	112	10	27
All ages	Pneumonia	Finland	1962–1963	Complement fixation	246	16	32
All ages	Pneumonia	Washington	1963–1964	Complement fixation	360	12	1
All ages	Pneumonia	Holland	1961–1966	Fluorescent antibody	320	33	31
All ages	Pneumonia	Sweden	1962–1963	Complement fixation	107	33	2
Military							
Marine recruits	Pneumonia	North and South Carolina	1959–1965	Fluorescent antibody, complement fixation, growth-inhibiting antibody	1369	38	7
Naval recruits	Pneumonia	Illinois	1959–1961	Complement fixation	294	8	11
Air Force recruits	Pneumonia	Mississippi	1959–1966	Complement fixation	772	47	43

Table 3. *Importance of M. pneumoniae in Respiratory Tract Disease According to Age.* (Infection Detected by Complement Fixation)

AGE (years)	LOWER RESPIRATORY TRACT ILLNESS						UPPER AND LOWER RESPIRATORY TRACT ILLNESS	
	District of Columbia (1962–1963)		Helsinki, Finland (1962–1963)		Seattle, Washington (1963–1964)		Sweden (1962–1963)	
	No. Ill	% Pos.	No. Ill	% Pos.	No. Ill	% Pos.	No. Ill*	% Pos.*
0–4	897	1	56	4	100	6	14	0
5–9	73	1	42	29	17	3	13	38
10–29	39	10	72	27	54	22	61	33
30–49	211	1	35	9	65	18	38	21
50 or >	179	4	52	8	72	0	113	3

*Approximate; original data presented with slightly different age groupings.

Table 4. *Clinical Signs and Symptoms of Patients with M. pneumoniae Pneumonia*

CLINICAL SYMPTOMS AND SIGNS	PER CENT OF PNEUMONIA PATIENTS WITH INDICATED FINDING			
	South Carolina (1959–1960)	Finland (1962–1963)	Sweden (1962–1963)	Washington (1963–1964)
Cough	93	100	100	100
Headache	84	33	45	75
Chills	78	–*	17	64
Malaise	74	–	–	83
Sore throat	53	–	13	50
Nasal symptoms	49	53	8	25
Fever	100	100	100	100
Rales	84	–	75	–
Cervical adenopathy	18	5	21	–
Pharyngeal erythema	12	–	48	–
Number studied	109	40	36	36

*Data not available.

However, in general, M. pneumoniae pneumonia has a longer incubation period and a more severe course than pneumonia caused by viral agents. In etiologically confirmed M. pneumoniae pneumonia,[1, 2, 32, 46] fever and cough are almost invariably present, and headache, chills and malaise are seen in a large proportion of patients (Table 4). The cough is dry and hacking but frequently productive of small amounts of greenish sputum. Sore throat and nasal symptoms are noted in approximately one-half of cases. Pharyngeal erythema and cervical adenopathy occur less frequently. Chest x-rays usually reveal minimal to moderate unilateral patchy infiltrates in the lower half of the lung. Upper lobe involvement or bilateral lower lobe involvement occurs in 25 per cent of patients. Lobar pneumonia, sometimes associated with pleural effusion, is an uncommon finding. Upper respiratory tract disease caused by M. pneumoniae is indistinguishable from disease caused by a variety of respiratory viruses.

The course of untreated M. pneumoniae pneumonia is usually long. Fever, headache, and malaise disappear three to ten days after onset of symptoms but pulmonary infiltration, cough, and rales sometimes persist for a month or more. Patients who are adequately treated demonstrate rapid clinical improvement, and fever usually disappears within one to three days following initiation of treatment. However, cough and abnormal chest findings may persist for a week or more.

In addition to myringitis and pleurisy the following pathologic conditions have been observed in patients presumably infected with M. pneumoniae: residual pleural thickening, interstitial emphysema, pericarditis, otitis media, otitis externa, perception deafness, meningoencephalitis, meningitis, erythema nodosum, pityriasis rosea, thrombocytopenic purpura, hemolytic disease, Stevens-Johnson syndrome and Guillain-Barré syndrome.[2, 15, 25, 28, 31, 40, 46, 47] The etiologic association of M. pneumoniae with these conditions remains to be confirmed in controlled studies.

Infection with M. pneumoniae is rarely fatal. In only three instances has the organism been recovered from the lung at autopsy.[17, 39]

Diagnosis and Serology

The diagnosis of M. pneumoniae infection is usually made retrospectively either by isolation of this slowly growing organism or by serologic procedures. Isolation of the organism is usually less efficient than serology. Several serologic techniques for the diagnosis of M. pneumoniae infection have been developed. The most important are listed in Table 5.

The most commonly used serodiagnostic test is complement fixation. Complement fixation antigens prepared from whole, broth-grown M. pneumoniae organisms usually contain residual medium components which are anticomplementary. Much of this anticomplementary activity can be removed by treatment with phenol.[9] However, a more potent CF antigen free of anticomplementary effects can be prepared from M. pneumoniae grown on a glass surface and washed free of medium constituents[61] or from a lipid fraction of the organism extracted with chloroform-methanol.[36]

Metabolism-inhibiting (growth-inhibiting) antibody is measured by its ability

Table 5. *Types of Serologic Response to Infection with M. pneumoniae*

RESPONSE	RELATIVE EFFICIENCY FOR SERODIAGNOSIS WHEN COMPARED WITH IMMUNOFLUORESCENCE TECHNIQUE	COMMENTS
Immunofluorescence of infected chick embryo lung	100%	Most sensitive and specific but laborious: requires pretesting of many infected embryos to find suitable antigen.
Complement fixation	90–100%	Antigen often anticomplementary; anticomplementary activity removed by treatment with phenol or extraction with lipid.
Indirect hemagglutination	90%	Measures the highest titers of antibody but is less specific than other methods.
Metabolic inhibition (growth inhibition)	90%	Growth-inhibiting antibody correlates better with protection from illness than antibody measured by other means.
Cold agglutinins	40–50%	Much less sensitive than other techniques. False-positive and false-negative results common.
Agglutinins of Streptococcus MG	10%	Relationship demonstrated between the two organisms by serology but not by DNA homology techniques.

to inhibit fermentation of carbohydrates[69] or reduction of 2,3,5-triphenyl tetrazolium by M. pneumoniae.[33] Metabolism-inhibiting antibody correlates better with resistance to illness than does antibody measured by other means.[70] For this reason this antibody has been used extensively for evaluation of experimental vaccines.

Cold agglutinins develop in approximately one-half of patients with M. pneumoniae pneumonia.[19] Furthermore, approximately one-quarter of cold agglutinin positive pneumonias cannot be related to M. pneumoniae infection. Recent evidence indicates that the soluble hemolysin of M. pneumoniae, identified as a peroxide, alters the I antigen of erythrocytes in vivo, rendering them antigenically foreign to man.[57, 60, 63] Cold agglutinins may represent an "autoimmune" response to such altered erythrocytes.[11]

A proportion of patients infected with M. pneumoniae develop agglutinins for Streptococcus MG (a ubiquitous oral bacterium).[71] A relationship between the two organisms has recently been demonstrated by complement fixation[38] but not by nucleic acid homology techniques.[11, 62] There is no evidence that M. pneumoniae is an L-form of Streptococcus MG.

The direct immunofluorescent staining of M. pneumoniae organisms in sputum and pleural fluid from suspected M. pneumoniae pneumonias has been reported.[30, 31] However, nonspecific staining limits the usefulness of this test. If perfected, the direct immunofluorescent test would provide the first clinically useful rapid diagnostic test for M. pneumoniae infection.

Treatment

In a double-blind study of 109 serologically proved M. pneumoniae illnesses 0.9 gm. of chlortetracycline daily for six days significantly shortened the duration of signs and symptoms when compared with untreated controls.[37] In addition, a course of 1 gm. of tetracycline or erythromycin per day in divided doses for seven days was employed successfully for the treatment of artificially acquired M. pneumoniae pneumonia in volunteers.[56] This regimen produced clinical improvement with diminution of fever in one to three days. Neither antibiotic eradicated the organism from the throat, and relapse with pneumonia nine days after tetracycline therapy was observed in one patient. There was no evidence of the emergence of drug-resistant strains in treated patients. In addition, these antibiotics attained levels in serum and nasal secretions that were sufficient to inhibit the organisms in vitro. Similar results with tetracycline therapy have been observed following natural infection.[24] At present we do not understand why tetracycline and erythromycin fail to eradicate the organism from man.

Prevention

The need for a vaccine for M. pneumoniae is indicated by the high incidence of pneumonia caused by this organism in civilian and military populations, the prolonged course of such illness, and the failure of antibiotics to eradicate this mycoplasma from the throat. Attempts to develop an attenuated live vaccine strain of M. pneumoniae have been discouraging. A preliminary investigation involving 50 volunteers suggested that the cultivation of M. pneumoniae on artificial medium resulted in attenuation of virulence for man.[13] Thus, organisms grown in artificial media produced significantly fewer febrile illnesses when administered to volunteers than did organisms grown in tissue culture. However, studies of two strains of M. pneumoniae in volunteers who lacked preexisting antibody suggested that infectivity for man also diminished when these organisms were serially passed in artificial medium. Thus, M. pneumoniae, strain FH, passed 12 times in artificial medium infected each of the nine volunteers who were challenged and produced illness in three. In contrast, the same strain passed 55 times in artificial medium infected only three of eight men but produced illness in each of these three persons. Similar results were obtained with the 1428 strain of M. pneumoniae.[56]

Attempts to prepare inactivated vaccines have been more successful. Initially the preparation of an inactivated M. pneumoniae vaccine was hindered by the low level of growth of M. pneumoniae in artificial medium and the presence of sensitizing medium components such as horse serum and beef heart infusion. These problems were solved by employing a well adapted strain of M. pneumoniae which grew to high titer in artificial medium and by substitution of tissue culture media and a chloroform extract of egg yolk for the serum components of the medium. The development of a concentrated vaccine prepared in such a way was recently reported.[34] The protective effect of the vaccine was tested in 19 volunteers who lacked detectable growth-inhibiting antibody prior to immunization.[56] Ten of the 19 men (53 per cent) demonstrated a serologic response to the vaccine following two injections. The 19 vaccinated volunteers and 13 seronegative controls were challenged with a virulent strain of M. pneumoniae. All the men were infected, as evidenced by recovery of the organism or a serologic response or both. However, only one of the ten men who developed vaccine-induced antibody became ill. In contrast, illness occurred in 10 of 13 men in the seronegative control group. Seven of the nine men who failed to respond to the vaccine also became ill.

A more extensive test of this vaccine was carried out among Marine recruits exposed to naturally acquired M. pneumoniae infection at Parris Island, South Carolina, and Camp Lejeune, North Carolina. A 46 per cent reduction in the rate of M. pneumoniae pneumonia was observed among vaccinees.[4]

Another killed M. pneumoniae vaccine was recently described in which the M. pneumoniae organisms were cultured in a "serum-free" medium to diminish unwanted antigenic medium components.[42] The vaccine was prepared in aqueous form and with alum or peanut oil adjuvants. When tested in human volunteers, all three vaccines were found to be antigenic. However, the alum and peanut oil vaccines stimulated a greater serologic response than did the aqueous vaccine. No controlled challenge experiments were reported. When administered to Air Force trainees at Keesler Air Force Base, Mississippi, the alum vaccine caused a 43 per cent reduction in the M. pneumoniae pneumonia rate among vaccinees.[43] It is difficult to compare the protective effects of the two vaccines just described because of differences in methods of preparation, administration, and testing, but it appears that they are of about equal, albeit low, potency. Nevertheless, they are prototype vaccines and they demonstrate that vaccine-induced protection from M. pneumoniae associated illness is feasible.

New techniques for the cultivation of M. pneumoniae and for the purification of mycoplasma antigens offer promise for the development of more potent vaccines. One such technique is the growth of M. pneumoniae on a glass surface.[61] The sheet of mycoplasmas attached to the glass can readily be washed to remove traces of medium, then scraped from the surface to yield a highly concentrated purified suspension of organisms suitable for use in vaccine production.

Recent studies of the antigens of M. pneumoniae indicate that most of the antigenic activity of the organism resides in a lipid moiety.[36, 38, 51, 58] This lipid antigen has been purified and identified as a low molecular weight lecithin-like compound.[50] It appears that this compound is a hapten that is capable of reacting with complement-fixing antibody and blocking growth-inhibiting antibody. Such a purified hapten, when conjugated with a carrier protein, may yield a suitably potent purified vaccine for the prevention of cold agglutinin-positive primary atypical pneumonia.

SUMMARY

Seven serologically distinct mycoplasmas (M. hominis type 1, M. salivarium, M. orale types 1, 2, and 3, M. fermentans, and M. pneumoniae) and a group of biologically similar but serologically heterogeneous mycoplasmas (the T-strains) infect man, but only M. pneumoniae is known to be an important cause of illness. M. pneumoniae is the etiologic agent of cold agglutinin-positive primary atypical pneumonia. It is responsible for 10 to 33 per cent of all pneumonias in civilian populations and 8 to 47 per cent of pneumonias among military recruits. M. pneumoniae causes a spectrum of illness ranging from inapparent infection to severe pneumonia of long duration. Tetracycline and erythromycin are effective in the treatment of M. pneumoniae pneumonia but they do not eradicate the organism from the respiratory tract. Attempts to develop killed vaccines to M. pneumoniae have been partially successful.

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Clinical Syndromes in Adults Caused by Respiratory Infection

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Most of the participants in this symposium have taken the point of view of the parasite. The genealogical background, biological characteristics, behavior in the laboratory, and spectrum of clinical effects for a number of etiological agents have been delineated and described. This is fitting and proper. Indeed, it is the manner in which textbooks are written. But the clinician faced with a diagnostic challenge in a sick patient must work from the clinical syndrome backward in seeking grounds for rational therapy. The array of signs and symptoms must be ascertained and placed in proper historical and epidemiological perspective, the probabilities of various causative agents weighed, and appropriate laboratory tests undertaken. In this situation the physician tries to deduce which pathogen might have produced the host response he has observed. It seems strange that the dynamics involved in this type of logic are just the opposite of the way most of us are taught – that of first learning the characteristics of the pathogen and secondarily of its effect in man.

The work of the investigator differs in these two approaches. The task of defining the clinical spectrum produced by a new respiratory agent is less formidable than the task of unraveling the total etiology of a given clinical syndrome. In the former, which one might call an agent seeking a disease, one isolation and/or serologic technique capable of identifying the new pathogen is employed using materials from patients with different clinical syndromes and appropriate appraisal made of its role in each. In respiratory diseases new clinical syndromes are rare so that generally one's task is completed in one session if adequate representation of the common clinical syndromes in different ages and years have been included. In the other approach the problem is one of a given syndrome seeking all possible causes. Here all types of isolation systems must be used, all known respiratory antigens included, and these methods applied simultaneously to materials from one or more clinical syndromes. Out of these data one constructs an etiological pie. Such pies, if not half baked from the start, may quickly

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become so in time because some antigen has been omitted. This is because new respiratory agents are being constantly discovered and to put them in proper perspective one should really retest the whole lot of old antigens together with the new agent or at least use materials from the same patients previously tested, if still salted away in the freezer. For these reasons investigation of the clinical syndrome is not so often undertaken and the information becomes rapidly outdated.

In spite of these limitations this presentation will start with the clinical syndromes of acute respiratory diseases in adults and work backward. Dr. Coriell will do the same for respiratory disease in children.[10] The syndrome of the common cold has been similarly discussed in these sessions by that able maestro of English rhetoric, runny noses, and rhinoviruses, Sir Christopher Andrewes.[3] Focus on the patient and the clinical syndromes of adults[16] and of children[11] also formed part of the program at the Conference on Newer Respiratory Diseases held at the National Institutes of Health in 1962 and of some other reports.[12, 33] I have also tried to deal with respiratory and other clinical syndromes of infectious disease in previous publications.[17, 19, 21, 25]

From a practical standpoint the physician must ask himself four questions in the diagnosis of a patient with a respiratory syndrome. These are:

1. How shall the syndrome be classified?
2. Is it viral or bacterial?
3. What laboratory tests should I request to establish this?
4. If bacterial, what antibiotic should I use?

THE REALITIES

Let us start with certain basic concepts. Table 1 lists what I call "The Five Realities."

First any one bacterial or viral agent is capable of producing a variety of clinical syndromes whose severity may range from mild or even inapparent infections to one requiring hospitalization. Most of the respiratory pathogens are capable of producing anything from a common cold to pneumonia under appropriate circumstances. Some pathogens like the rhinoviruses may be highly prejudiced in their preferences for the upper respiratory tract and some such as M. pneumoniae may have equal prejudice for the lower respiratory tract, but under certain conditions the rhinovirus may participate in a pneumonitis and the mycoplasma in a mild upper respiratory infection, or even a myringitis. There are other respiratory agents, such as the adenoviruses, that are less fastidious as to the site of multiplication and tissue reaction. There are also groups of viruses whose natural habitat is elsewhere and whose

Table 1. *The Five Realities*

1. *The same clinical syndrome* may be produced by a variety of agents.
2. *The same etiologic agent* may produce a variety of clinical syndromes.
3. *The predominating agent* in a given clinical syndrome may vary according to the age group involved, the year, the geographic location, and the type of population (military or civilian).
4. *Diagnosis of the etiological agent* is frequently impossible on the basis of the clinical findings alone.
5. *The cause(s)* of a large percentage of common infectious disease syndromes are still unknown.

occasional interest in the respiratory tract has been belatedly recognized. I refer specifically to the Coxsackie and ECHO viruses. In the past we regarded these primarily as intestinal inhabitants with a special preference for the central nervous system. But herpangina and pleurodynia are also host responses to the enteroviruses and more recently these groups have been implicated in mild upper respiratory disease syndromes.

The second "Reality" of Table 1 is the exact reverse of that just discussed: It is that one clinical syndrome may result from infection with any one of a number of viruses, bacteria, fungi, or other pathogens. For example, the clinical syndrome of acute upper respiratory infection may result from influenza or parainfluenza viruses, from any one of a number of adenoviruses, from respiratory syncytial virus (usually reinfection in adults), from psittacosis, H. influenzae, or Mycoplasma pneumoniae. It may be the expression of such diverse organisms as dengue, leptospirosis, histoplasmosis, coccidioidomycosis, and tuberculosis; it may be the prelude to the more characteristic features of infection with measles or poliomyelitis viruses. The same holds true for many of the other common respiratory syndromes. The point is that the physician must consider a large number of possible etiological agents when faced with a patient with a respiratory infection, and weigh the probabilities as to which one is involved.

Thirdly, a great many factors influence the host response to a given pathogen. Some of these are listed alphabetically in Table 2. Age is probably the most important because it reflects not only tissue susceptibility but also the presence or absence of immunity from prior infection. Bronchiolitis and croup are clinical responses to respiratory syncytial and parainfluenza virus in the child that are not seen in the adult. Reinfections may occur in the adult but are usually mild and upper respiratory. The varying host response to streptococcal infection at different ages recognized first by Powers and Boisvert[44] is another example; in this there is an increased severity and greater localization of infection from infancy to the young adult, whose clinical expressions range from mild nasopharyngitis to severe tonsillitis and otitis media. Some clinical syndromes are highly characteristic of a given age group. For example, infectious mononucleosis is a disease of the young adult, and mycoplasma pneumonia of the late teens. Genetic predisposition is another factor of emerging importance: acute respiratory infections are not only more common in certain families than in others living under the same environment but also some tend to respond to a given pathogen with upper respiratory symptoms and others with lower respiratory symptoms. Some people get head colds and others get chest colds. Smoking and allergy may also influence the site of involvement. Allergy

Table 2. *Factors Affecting the Host Response to Respiratory Pathogens*

1. Age
2. Allergy
3. Coexisting pulmonary or cardiac disease
4. Environmental setting (institution, family, etc.)
5. Genetic predisposition
6. Geographic location
7. Immunity and prior exposure
8. Occupation (civilian vs. military recruit)
9. Physiologic and psychological state
10. Season and year
11. Smoking
12. Tropism of the agent

seems to accentuate the symptoms of a common cold.[35] Geography is also important: pathogens predominate in different areas at different times and in different seasons. Acute respiratory patterns are much different in the military recruit than in the university student of the same age: adenovirus infections are very common in the soldier but of little consequence in the student.[18, 48] Knowledge of these various epidemiological factors and of the basic tropism of the agent are often more useful in making a differential diagnosis than the clinical signs and symptoms.

Physiological and psychological factors also influence the host response. For example, women are most susceptible to the common cold in the middle period between menses and most resistant during the period of menstruation.[34, 35] Chilling is a factor of some controversy: despite the firm opinion of our mothers, grandmothers, and the general public (including myself) that chilling, cold feet, and drafts bring on a cold, neither Dr. Andrewes nor Dr. Jackson and their associates have been able to substantiate this in experiments with human volunteers.[2, 35] Recently evidence that psychological factors may play a role in the host response to infection with influenza viruses, and perhaps even to infection itself, has been shown by Cluff et al.[8] Part of this may simply reflect the fact that some people complain about everything and others are highly stoical and fail to admit they are ill.

The fourth "Reality" of Table 1 emphasizes the limitation in our diagnostic capabilities. The capacity of the respiratory tract to respond to infection is a limited one – edema, exudation, and inflammation are the common tissue responses. These morphological reactions are reflected in a limited number of signs and symptoms: cough, soreness, redness, and obstruction. In children bronchial spasm and wheezing are common, producing bronchiolitis and the croup syndrome. The variations in these themes produced by a given pathogen are related to the anatomical area chosen and the severity of involvement. Such variations may not be of sufficient magnitude or sufficiently characteristic to enable the physician to tell one pathogen from another.

The last reality will be discussed in detail later.

CLINICAL CLASSIFICATION

In the light of present knowledge the simplest classification may be the most useful. This involves the recognition of the anatomical area most involved (Table 3). While a strict anatomical terminology such as

Table 3. *Clinical Classification of Respiratory Syndromes in Adults*

ANATOMICAL DESIGNATION	COMMON SYNONYMS	MAJOR ETIOLOGICAL AGENT
Nasopharyngitis	Common cold	Rhinoviruses
Pharyngotonsillitis	Acute tonsillitis, acute pharyngitis	Hemolytic streptococcus group A
Upper respiratory	Acute URI, "ARD," influenza, la grippe	Influenza
Lower respiratory	Bronchitis, pneumonitis, primary atypical pneumonia	Mycoplasma pneumoniae

URI, upper respiratory infection. ARD, acute respiratory disease.

Table 4. *Clinical Classification of Common Respiratory Disease in Hospitalized University of Wisconsin Students*

No. of admissions Period of study	2331 1949–1954	2549 1960–1965
CATEGORY	PER CENT DISTRIBUTION	
Acute upper respiratory infection	36.0*	24.4
Bronchitis	5.0*	7.4
Infectious mononucleosis	21.5	36.4
Pharyngotonsillitis	27.9	18.8
Pneumonitis	5.8	11.4
Pneumonia	3.8	1.6
TOTAL	100	100

(From Evans, A. S.: New England J. Med. 256:377, 1957, and unpublished data.)

*Breakdown estimated in light of later data.

"nasopharyngitis" may be theoretically desirable, the wide usage of the term "common cold" makes a change in terminology undesirable. Similarly the term "acute upper respiratory infection" seems better than the anatomical designation of pharyngotracheobronchitis. The point is that a simple anatomical separation of the common clinical syndromes may be all that is possible. Specific features can then be added when observed such as the ulcerative mouth lesions of Coxsackie infection, or the palatine petechiae of infectious mononucleosis. Popular usage of presumed etiological diagnoses such as "influenza" or "strep throat" based on clinical findings *alone* is too frequently wrong to be useful and just adds to the confusion. It should be discontinued.

The relative frequency of different clinical syndromes in hospitalized young adults is given in Table 4 based on over 5000 admissions of University of Wisconsin students in two periods of time.[17, 26] Acute upper respiratory infections, infectious mononucleosis, and acute pharyngotonsillitis lead the list. In the last ten years infectious mononucleosis and pneumonitis have gained in importance. Past the college age the pattern of hospital admissions for respiratory disease is one with more lower respiratory involvement, with pneumonia predominating. In office practice acute upper respiratory infection would probably dominate the picture in all age groups.

TOTAL RESPIRATORY PATTERN

Our knowledge of the etiology of common respiratory diseases has gradually increased. The most important recent advances have been the discovery of rhinoviruses and their importance in the common cold syndrome and of M. pneumoniae in lower respiratory infections. An estimate of the present situation for total respiratory disease is given in Figure 1 for adults. The variation between mild and severe infection is portrayed in Figure 2. About 60 per cent of the etiological agents can be identified and 40 per cent are unknown. These estimates are based on our own work and that of others.[16, 17, 29, 31, 33, 37, 39] Different agents vary in their importance in different clinical syndromes. This is shown in Figure 2a which schematically presents this interplay between etiological agents and clinical syndromes.

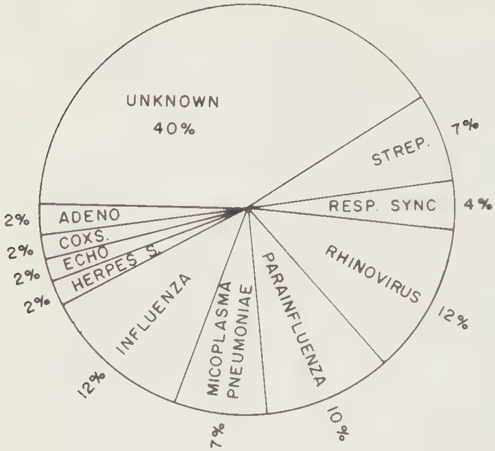


Figure 1. Etiological pie for total acute respiratory syndromes in adults. (Estimate of data as of 1966.)

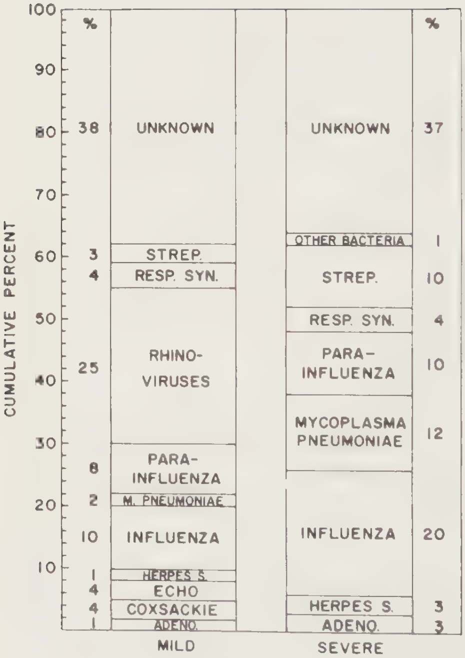
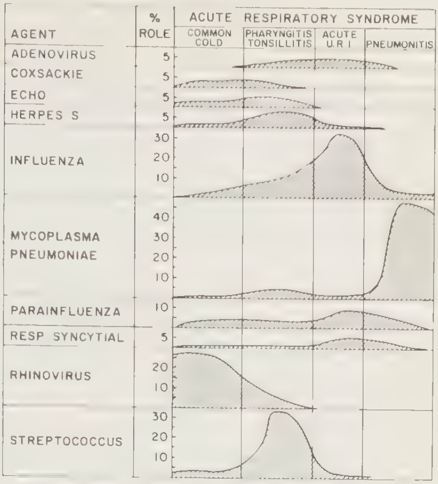


Figure 2. Estimated relative role of respiratory pathogens in adults, 1966.

Figure 2a. Etiological agents and clinical syndromes of respiratory infections in adults.



ETIOLOGIC AGENTS AND CLINICAL SYNDROMES IN ADULTS

The clinician can better pinpoint the etiological probabilities if the specific clinical syndrome is considered and I will now discuss these individually.

SPECIFIC CLINICAL SYNDROMES

Common Cold

Next to hangovers, women, and taxes this is man's most important affliction. Dr. Andrewes has discussed this syndrome in detail,[3] so I will pass over it very briefly. Recognition of the clinical picture presents no problem and the patient's own diagnosis is usually reliable. For years investigators sought the key to the door that would reveal the cause of the common cold. The search was finally rewarded in 1956 by the independent discovery in two separate laboratories of what is now called the rhinovirus group.[42, 45]

The next ten years led to much information on the growth, biologic properties, and laboratory recognition of these agents,[28] but delineated several very difficult problems in the application of this knowledge to the prevention of the common cold. First, there were 55 or so *separate* antigenic types identified, each of which might be a candidate for inclusion in a vaccine. Second, these agents were associated with only about 25 per cent of cases of the common cold, with a range of 10 to 30 per cent.[14, 28–35, 37] All age groups were affected but the rhinoviruses were less common in children. In adults other viruses such as parainfluenza, respiratory syncytial, and Coxsackie viruses, while capable of producing the common cold syndrome, accounted all together for less than 10 per cent of cases. This left 60 to 70 per cent of the causative agents yet to be discovered. Third, no single rhinovirus type seems to predominate and thus become the "best candidate" for a vaccine. Because of the difficulties of identifying the serotypes, epidemiologic information is yet sparse on the behavior of any single rhinovirus over any period of time; but it is clear that in any season a large number may be active at the same time.[14, 28] In our study of graduate students and their families at the University of Wisconsin, Dr. Dick and I found one strain quite predominant one year, but the next year it disappeared.[11] Two rhinovirus types were found associated with the common cold in the same family at the same time. Fourth, the signs and symptoms of colds associated with rhinoviruses do not differ appreciably from those associated with other agents or those of unknown etiology. However,

Table 5. *Diagnostic Criteria for Infectious Mononucleosis*

Clinical Picture: Fever, sore throat usually with exudate, posterior cervical lymphadenopathy, and splenomegaly (in about 50 per cent).

Blood Picture: Lymphocyte-monocytes over 50 per cent with at least 10 per cent atypical forms.

Hepatic Involvement: Manifested by abnormal cephalin-cholesterol flocculation and elevated serum transaminase levels, esp. LDH.

Heterophile Titer Elevation: Increase of sheep cell (heterophile)* agglutinins which persist after absorption with guinea pig kidney.

*Heterophile antibody not an *essential* diagnostic criterion.

Table 6. *The High Priority Group for Penicillin*

A sore throat as the primary complaint and *one* or more of the following:

1. *History* of rheumatic fever or acute glomerulonephritis in the patient or his family, or of previous episodes of streptococcal sore throat.
2. *Presence* of exudate, marked redness and edema, otitis media, or leukocytosis over 13,000/cu.mm.
3. *Absence* of runny nose, hoarseness, and cough.
4. *Coexistence* of other chronic illness such as diabetes, heart disease, and chronic pulmonary disease.

rhinoviruses are primarily associated with the common cold and mild upper respiratory disease in adults and play little or no role in other clinical syndromes of respiratory infection. Finally, the role of nasal vs. humeral antibody in disease protection needs clarification as a guide to a choice between a live nasal vaccine or an inactivated parenteral vaccine.

Acute Pharyngitis and Tonsillitis

The syndrome of sore throat with fever involves the clinical differentiation in the young adult between streptococcal sore throat, nonstreptococcal sore throat, and infectious mononucleosis. First let us deal with infectious mononucleosis, because the clinical features and laboratory tests permit diagnosis albeit the early findings and the appearance of the throat may be indistinguishable from other forms of sore throat. This syndrome represented 45 per cent of 739 students admitted to the University of Wisconsin infirmary with sore throat.[24] Four diagnostic criteria are listed in Table 5. I do not regard an elevated heterophile titer essential to diagnosis. In addition, the presence of palatine petechiae in 25 per cent, a distaste for cigarettes in the smoker, and fist percussion tenderness over the liver are important clues. No causative agent has been identified in infectious mononucleosis.

The etiological causes of other forms of sore throat are given in Figure 3 based on a study of 308 hospitalized students: one-third are associated with the hemolytic streptococcus, another third with a variety of viruses, and the remainder are of unknown cause.[24] The clinical differentiation of these types is difficult and generally unreliable. Neither the presence of exudate nor of leukocytosis differentiates streptococcal from nonstreptococcal pharyngotonsillitis in individual patients. A throat culture is mandatory for definitive diagnosis and intelligent therapy and is now widely available through hospitals and clinics and through the services of public health laboratories.

The following management is suggested: (1) take a throat culture; (2) initiate therapy with procaine or oral penicillin in the high priority group (Table 6) in whom the susceptibility to nonsuppurative or suppurative complications is high; (3) give Bicillin or continue oral therapy

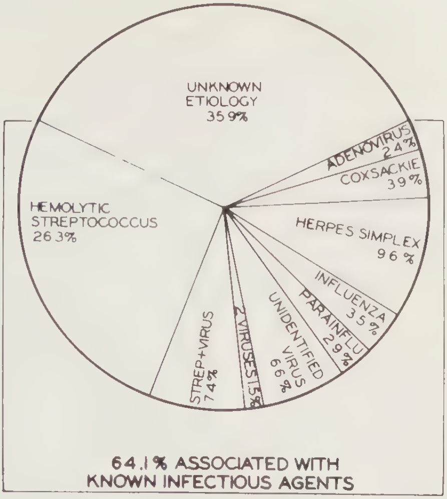


Figure 3. Distribution of etiologic agents associated with acute pharyngitis-tonsillitis in 308 hospitalized patients ("maximal" estimate). (From Evans, A. S., and Dick, E. C.: J.A.M.A. *190*:699, 1964.)

for a total of ten days (not *less*) if the throat culture is positive and discontinue penicillin if the throat culture is negative. Always use penicillin unless sensitivity exists, then use erythromycin over a ten-day period to eliminate the streptococcus whose persistence may lead to rheumatic fever.

Acute Upper Respiratory Infection

This syndrome variously called "influenza," ARD, etc., constitutes the major segment of patients with respiratory disease seeking medical care. This diagnosis constituted about 30 per cent of 5000 respiratory admissions of young adults to the University of Wisconsin infirmary.[17, 23, 26] It is an undifferentiated clinical picture whose classification is based largely on the *absence* of predominating features: thus the nose doesn't run enough, the throat is not sore nor red enough, and the cough is not severe nor paroxysmal enough to classify the illness as one of the other respiratory syndromes. Fever is a constant feature and generalized aching and malaise are almost always present. Physical signs are sparse but redness of the throat and occasional rales may be present.

There are no clear-cut clinical features pointing to a specific etiological agent. When there is a cluster or a growing wave of patients with this undifferentiated acute respiratory picture, particularly when muscle aching and prostration occur commonly, then a true outbreak due to influenza virus is usually suspected. In periods of this type a laboratory diagnosis of influenza can be established for 80 per cent of patients with this clinical syndrome.[23] In nonepidemic periods, infections with influenza virus may account for only 10 to 20 per cent of acute upper respiratory infections. In any event, influenza virus is the predominating etiological agent in acute upper respiratory infection; in 398 Wisconsin students admitted to the infirmary with this diagnosis from 1953 to 1962, serologic evidence of influenza virus infection was detected in 34 per cent.[23] Parainfluenza viruses are next in importance in young civilian adults with this syndrome,[6, 13, 20] constituting 2 to 9 per cent. If mild cases are included, then the rhinoviruses will play a significant role. Adenoviruses constitute less than 3 per cent and respiratory syncytia perhaps 4 per cent of the upper respiratory infection syndrome in civilian adults.[17, 18, 48] Bacterial agents have not been shown to be of importance in this syndrome, so that antibiotic therapy is neither warranted nor useful.

The etiological spectrum is different in military recruits with acute upper respiratory disease, or "ARD" in Army terminology. Here the adenoviruses are a very important cause of the order of 30 to 50 per cent or so.[48] Variations occur from one camp to another and from one season to another.[46] Influenza virus is the next most important cause of ARD in military recruits, also varying from year to year. The streptococci are also sometimes reported as important in ARD, because the category of pharyngotonsillitis is included in the category of "ARD" by some users of military parlance. Certainly it is an important cause of sore throats in the military, however this syndrome may be classified.

Antibiotics are not effective in acute respiratory infections because most are due to viruses. Attention must be directed at prevention. An influenza vaccine which incorporates current strains will lower the incidence of acute upper respiratory infection as this virus plays an important role in its causation. In military recruits adenovirus vaccine has been successful, both in a parenteral killed preparation[48] and more recently a live oral vaccine,[11] but no commercial preparation is currently available.

Acute Lower Respiratory Infection

This clinical syndrome includes bronchitis, pneumonitis, and pneumonia. In young adults the predominating clinical syndrome is that of pneumonitis characterized by a paroxymal cough and by blotchy densities on x-ray; this form is popularly called primary atypical pneumonia. Figure 4 depicts the etiological agents involved in young civilian adults as of 1961.[22] In more recent studies with better techniques the role of M. pneumoniae has been placed at 40 to 60 per cent.[7, 26] Varia-

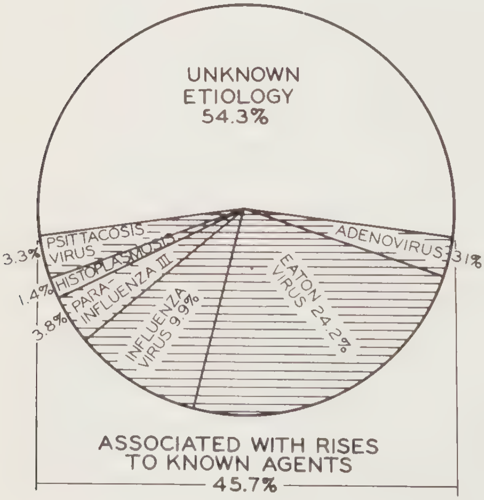


Figure 4. Distribution of etiologic agent associated with acute lower respiratory tract infection in hospitalized students as of 1961. Eaton virus is now recognized as M. pneumoniae. (From Evans, A. S., and Brobst, M.: New England J. Med. 265:401, 1961.)

tions occur from year to year and there is evidence of a four- to five-year cycle of high incidence.[26] Outbreaks tend to occur in the fall. Rates of 1 to 1.5 per 1000 per year for clinically recognizable pneumonia due to this have been found in a large study in Seattle, Washington, for the period from December, 1963 to December, 1964.[1] The tendency of M. pneumoniae pneumonitis to involve family units should be emphasized.[1,9] The organism spreads slowly but in the course of time most susceptible family members become infected. The infection is often introduced by the school child. Indeed, the peak incidence of infection is in the 5- to 19-year age group.[1] Under age 5 and over 40 Mycoplasma pneumonia is rare. Figure 5 shows the age distribution in a civilian outbreak we studied in La Crosse;[9] note the high frequency in the 5–14 age group.

The etiological pie of acute lower respiratory disease in recruits is also dominated by M. pneumoniae in many training camps. In Marine recruits at Parris Island, for example, Mycoplasma pneumoniae (or Eaton agent) was found alone in 37.6 marines with pneumonia and in association with another agent in another 8.3 per cent for a total involvement of 45.9 per cent (Fig. 6).[38] In naval recruits at Great Lakes Training Station M. pneumoniae has accounted for only 10 per cent of pneumonia.[46] So much for etiology.

The differential diagnosis of infections due to M. pneumoniae from the pneumonias of all other causes is very difficult. Table 7 compares the findings in University of Wisconsin students.[26] The fever tends to be higher and leukocytosis less in Mycoplasma-positive cases but no basis for clear differentiation is apparent. In other studies, coryza and leukocytosis have been more common in the pneumonias due to other

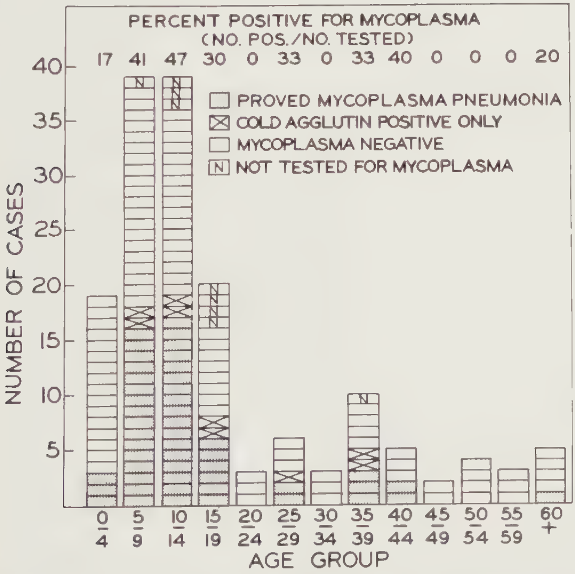


Figure 5. Age distribution of pneumonia due to M. pneumoniae and other agents in La Crosse, Wisconsin, 1965. (From Copps, S. C., Evans, A. S., Allen, V., and Sueltmann, S.: A community outbreak of mycoplasma pneumonia in La Crosse, Wis. Am. Rev. Resp. Dis., in press.)

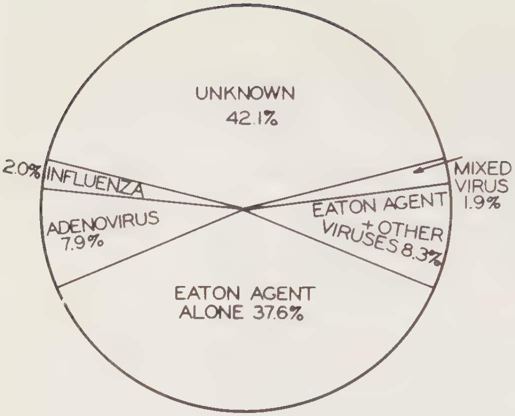


Figure 6. Etiological pie in 290 Marine recruits with viral pneumonia, Oct., 1959, to May, 1960. (From Kingston, J. R., et al.: J.A.M.A. *176*:118, 1961.)

causes.[1] The presence of an elevated or rising titer to cold agglutinins is the best simple guide to pneumonia due to M. pneumoniae; 72–92 per cent of cold agglutinin-positive pneumonias develop specific antibody to M. pneumoniae.[7] The importance of the recognition of Myoplasma pneumonia is the proved response to broad-spectrum antibiotic therapy. This was firmly established by Kingston et al.[38] in carefully controlled double blind studies of tetracycline therapy in 109 pneumonias serologically positive for M. pneumoniae. Other agents involved in the nonbacterial or virus pneumonia syndrome do not respond to antibiotics.

In older adults, bacterial pneumonia is clearly the important form of acute lower respiratory disease, but few viral studies have been done in this age group. An analysis of 2871 adult admissions for pneumonia published in 1959[5] showed about 20 per cent to be associated with known bacteria, of which the pneumococci represent 10 per cent, and another 48 per cent were attributed to unknown bacteria, for a total of

Table 7. *Major Signs and Symptoms in Pneumonia Due to M. Pneumoniae Compared to Pneumonia of Other Causes in University of Wisconsin Students*

	M. PNEUMONIAE POSITIVE	M. PNEUMONIAE NEGATIVE
No. in group	59	63
	Per Cent Positive	
Symptoms		
Cough	78	74
Chilliness	41	36
Sore throat	37	33
Coryza	22	16
Generalized aches	22	13
Signs		
Fever over 103° F.	46.4	26.8
X-ray abnormal	89	80
Rales	22	19
Leukocytes > 10,000	19.8	42.4

68 per cent bacterial; the rest were called viral or atypical pneumonia. No viral or mycoplasma studies were done. The classification into unknown bacterial and the viral or atypical category was based mainly on whether the white blood cell count was over or under 10,000 per cu. mm. We know this now to be an unreliable indicator of whether an infection is viral or not. A more recent study is that of 197 pneumonia admissions to the Cook County Hospital from 1963–1964;[36] 75 per cent were classified as bacterial, 12 per cent atypical or viral, 5 per cent tuberculosis, and 8 per cent represented other types of chest disease. Again no viral studies were done but culture and serology were performed for the mycoplasma. Only one isolate of M. pneumoniae was made but 20 per cent of 118 paired sera tested were positive for this organism by the TRI (tetrazolium reduction inhibition) test and 9 per cent by the CF (complement fixation) test. The low isolation rate was attributed partly to tetracycline therapy prior to admission.

THERAPY

Only two significant decisions on antibiotics need be made in treating young adults with acute respiratory disease (Table 8). All other infections are viral or at least nonbacterial and do not respond to antibiotic therapy. The first decision is whether to use penicillin (over a ten-day period) for the treatment of the patient with sore throat. The factors influencing this have already been discussed and I wish only to re-emphasize that the only reliable diagnosis is based on the results of a throat culture. The second decision is whether to employ tetracycline in the young adult with pneumonitis or pneumonia. The question is whether it is due to M. pneumoniae and will respond or is viral and will not. Here the isolation of the agent takes too long to be useful as a basis for therapy and serologic tests including the cold agglutinin test usually become positive too late for practical purposes. The decision must therefore be based on a few clinical leads, the severity of the case, and on epidemiologic grounds. The epidemiologic grounds include a cluster of cases of pneumonitis, some of which are cold agglutinin positive, the occurrence of cases in the fall of the year, and a high incidence in the 5- to 20-year age group. A third decision is involved in treating pneumonia in middle-aged and older adults: here one must decide both whether to give an antibiotic and the specific antibiotic to be used. Both decisions will be greatly facilitated by doing an immediate Gram stain on a thick portion of a good sputum specimen and sending in a culture. Then the initial antibiotic can be changed, if need be, on the

Table 8. *Summary of Management of Acute Respiratory Disease in Adults*

CLINICAL SYNDROMES	MANAGEMENT
Common cold	Bed rest, avoid antibiotics
Pharyngotonsillitis	Penicillin over 10-day period when culture is positive for beta hemolytic streptococcus
Acute upper respiratory infection	Bed rest, cough medicine, aspirin
Acute lower respiratory infection	Tetracycline for 5 days if severe or if M. pneumoniae is suspected

basis of the cultural and antibiotic results. The details of such management are well presented in texts and articles.[4, 27, 49]

PREVENTION

The main approach to control of acute respiratory disease today lies in efforts to develop vaccines. These are summarized in Table 9 and have been dealt with in detail by other participants in this symposium. There are many technical problems which include the multiple antigenic strains in groups like the rhinoviruses and adenoviruses, the low antigenicity of many preparations thus far like early parainfluenza and respiratory syncytial vaccines, the desirability of live vs. killed vaccines, the exclusion of contaminating tissue culture viruses, and the oncogenic properties of some agents for hamsters. Over and beyond these technical issues are such basic problems as: (1) Does the pathogen in question contribute significantly enough to respiratory disease to justify a big vaccination program. (2) Is annual vaccination needed? (3) What side effects to vaccination are there? These questions and many others remain to be answered. The hopeful new developments include trials of live vaccines, multiple killed vaccines combined with an effective adjuvant, and viral chemotherapy.

Table 9. *Summary of Prevention of Acute Respiratory Disease in Adults*

ETIOLOGICAL AGENT	STATUS OF VACCINE	USE IN ADULTS
1. Adenovirus	Oral vaccine promising and effective. Parenteral vaccine off the market	Military recruits; none in civilians
2. Influenza	Polyvalent vaccine available	Military recruits; special risk civilians
3. Mycoplasma pneumoniae	Formalin-killed and live vaccine under study	Military recruits; special risk civilians
4. Parainfluenza	Polyvalent vaccine under trial	None (use in children)
5. Respiratory syncytial	Poor antigenicity of vaccines thus far developed	None (use in children)

SUMMARY

1. The common syndromes of respiratory disease have been discussed from the standpoint of classification, etiology, clinical recognition, and management.

2. One etiological agent predominates in most syndromes as follows: common cold – rhinoviruses 15 to 30 per cent acute pharyngitis-tonsillitis – beta hemolytic streptococcus 25 to 35 per cent; acute upper respiratory infection – influenza 15 to 35 per cent; acute lower respiratory disease – M. pneumoniae 25 to 60 per cent.

3. Estimates as to the frequency of different etiological agents in different clinical syndromes are given. Over all about 40 per cent of the common clinical syndromes of respiratory infections can be identified etiologically; the causes of the other 60 per cent remain to be discovered.

4. The decision to use specific antibiotic therapy is involved in only two clinical syndromes of young adults: whether to use penicillin for acute pharyngotonsillitis and whether to use tetracycline for acute lower respiratory disease. The factors influencing these decisions have been discussed. In older adults the question of *which* antibiotic to use in bacterial pneumonia is involved and is dependent on laboratory work to identify the particular organism involved.

5. Prevention of respiratory disease is progressing slowly through a maze of technical problems and a multiplicity of antigenic types.

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Clinical Syndromes in Children Caused by Respiratory Infection

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Identification of respiratory infectious diseases by the clinical manifestations without reference to the etiology (syndrome) is a time-honored and practical method of referring to this group of diseases.

It has long been apparent that the known bacterial pathogens account for less than 10 per cent of acute respiratory disease in childhood,[1, 2] and this proportion has been getting smaller in recent years with the reduced incidence of tuberculosis, diphtheria, and streptococcosis. It has long been assumed that the majority of acute respiratory diseases are caused by viruses. During the past 15 years over 136[3] viruses capable of causing respiratory diseases have been identified and the list is still growing. In careful studies of infections in college students and military recruits, a specific cause could be determined in 85 per cent, of which 72 per cent were viral and 7 per cent were due to Mycoplasma pneumoniae.[18] In contrast, only about 50 per cent of respiratory tract infections in infants and children can be associated with the presence of a virus or mycoplasma.[3] It seems clear that additional viral and possibly other causes of respiratory illness in children remain to be discovered. One of the remarkable features of respiratory diseases in infants and children is that so many different agents can cause diseases that are clinically indistinguishable. This justifies the continued use of the term "disease syndrome" in referring to this group of diseases rather than the use of specific etiologic designations. However, this paper will attempt to correlate the newer knowledge of etiology with the classic clinical syndromes of respiratory disease in childhood.

The classic respiratory syndromes in infancy and childhood include otitis media, the common cold, bronchitis, croup, bronchiolitis, and pneumonia. Typically, each person has repeated episodes of the same type of illness but this varies widely and there are many conditioning factors, including individual, geographic, climatic, social, and economic. A partial explanation for the recurrences is the large number of agents and antigenic variants within each group of agents, but much more information is needed to explain the complex epidemiology and pathogenesis of respiratory disease. The incidence of respiratory infection

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Table 1. *Agents That Cause Respiratory Disease in Infants and Children**

	STRAINS	OM	URI	BRONCHITIS	CROUP	BRONCHIOLITIS	PNEUMONIA
Myxovirus							
influenza	3	?	++	+	+	+	+
parainfluenza	4	?	+++	+++	+++	++	++
resp. syncytial	1	?	+++	+++	++	++++	++++
Adenovirus	31	?	+++	++	+	++	+++
Picornavirus							
Coxsackie A	23	?	++				
Coxsackie B	6	+	++				-
rhinovirus	60+	∓	++	++		+	+
Mycoplasma	8	+	+	++		+	++
Bacteria							
pneumococcus	75	++	+				+
H. influenzae	6	++	∓	+	+		∓
beta hemolytic streptococcus	40	∓	++				∓
other	10+	∓	∓				∓
	267						

*Modified from Chanock, R., and Parrott, R.: Acute respiratory disease in infancy and childhood. Relative importance graded on a scale from 0 to ++++. Pediatrics 36:21, 1965.

OM, Otitis media. URI, Upper respiratory infection.

has been reported as 6.2 illnesses per person per year, being most frequent in winter and lowest in summer.[19]

The most common etiologic agents identified with respiratory disease in childhood fall into five groups: myxoviruses, adenoviruses, picornaviruses, mycoplasma, and bacteria (Table 1). Each of the virus groups and some of the bacteria may cause each clinical syndrome and therefore an etiologic diagnosis cannot be made with certainty without laboratory confirmation. Both virus isolation and acute and convalescent sera are necessary to confirm the diagnosis of a virus disease and even then interpretation may be difficult because the patient may be harboring viruses other than the one responsible for the acute illness.[10] This is particularly true of the adenoviruses and rhinoviruses. Furthermore, a high antibody rise to a past infection may be triggered by a current infection with a different but related virus, the "original sin" reaction. Because of the multiplicity of agents, the diagnosis of sporadic respiratory infections is quite unreliable without laboratory confirmation. However, in an epidemic, when the prevalent virus has been demonstrated by laboratory tests, it may be possible to approximate a reasonable percentage of etiologic diagnosis on the basis of clinical observation.

Infections with influenza A and B, respiratory syncytial virus, and beta hemolytic streptococci tend to occur in epidemics at yearly or longer intervals. Parainfluenza and rhinovirus infections are characteristically endemic. Adenovirus infections are usually endemic but types 3 and 7 can cause sharp outbreaks among children.[11] Mycoplasma infections are characteristically endemic and tend to spread slowly through a family or population.[12] Chanock and Parrott[3] have estimated on the basis of a seven-year study of respiratory diseases in a children's hospital that 9 to 14 per cent were caused by respiratory syncytial virus, 7 to 16 per cent by parainfluenza viruses, 8 to 9 per cent by adenoviruses, 4 to 5 per cent by rhinoviruses, and 1 per cent by Mycoplasma pneumoniae. Others have observed a higher incidence due to mycoplasma in preschool and school-age children[12, 23] The incidence in children who stay at home may vary considerably from these figures observed in hospitalized children, as it may also for any short period, or for a season—any one of these viruses may cause a much higher percentage of total respiratory disease.

CLINICAL SYNDROMES

Otitis Media

Otitis media is treated here as a separate syndrome, rather than as a complication of other infections, to draw attention to the absence of good virologic studies. Studies from several countries are in general agreement that pathogenic bacteria can be grown from the fluid of acute otitis media in about 50 per cent of cases.[4–7]

In needle-aspirated middle-ear fluid, Diplococcus pneumoniae is the most frequent organism in the childhood age group. In infants under three years of age Haemophilus influenzae, type b, is a close second but it is very rarely seen as a cause of otitis media in patients over four years of age. Other organisms are occasionally seen including beta hemolytic streptococcus, Staphylococcus aureus, Pseudomonas aeruginosa, and mixed infections of two or more bacteria. Coxsackie B4 has been grown from aspirated fluid[8] and Mycoplasma pneumoniae has been observed in bullous myringitis and purulent otitis media.[6, 9] Nasopharyngeal and throat cultures are reliable in not more than 50 per cent of cases in identifying the organism found by needle aspiration of the middle ear. No studies have been published in which a systematic search has been made for viruses, mycoplasma, and bacteria in the same aspirated fluid of otitis media. These are awaited with interest because present fragmentary knowledge suggests that mycoplasma may be a significant cause of otitis media, in childhood as well as in young adults. Since viruses are by far the major cause of upper respiratory infections that usually precede otitis media, it would not be surprising to learn that viruses and the mycoplasma are the basic etiologic factors in practically all otitis, with the bacteria sometimes acting as secondary invaders. It is too bad that in spite of all the careful bacteriologic and viral studies on the etiology of respiratory infections no group of investigators has so far applied both techniques to the same clinical specimens; such a collaborative effort should be quite revealing in otitis media.

Therapy of otitis media should be adequate to control pneumococci and Haemophilus influenzae and should be continued until the infection has subsided; a myringotomy should be performed to relieve pain and fever and to prevent spontaneous rupture if the eardrum is bulging.

Upper Respiratory Disease (Acute Nasopharyngitis, Nondifferentiated Acute Respiratory Disease, Common Cold)

Most acute upper respiratory infections are caused by viruses, including those that cause predominantly nasal symptoms and those

Table 2. *Isolations from Cases by Age Groups**

VIRUS	AGE 0–1	1–5	6–10	11–16
Influenza	–	9	5	7
Parainfluenza	15	31	9	1
Respiratory syncytial	30	19	1	–
Adenovirus	10	36	26	6
Herpes simplex	3	11	6	3
Enterovirus	11	45	20	5
Rhinovirus	10	25	9	5
Unidentified	1	7	2	2
Beta hemolytic streptococci	1	28	45	17
TOTAL STUDIED	275	641	362	143

*Modified from Tyrrell, D. A. J., et al.: A collaborative study of the etiology of acute respiratory infections in Britain. 1961–4. Brit. Med. J. 2:319, 1965.

that cause pharyngeal exudate, fever, and adenopathy. Bacterial secondary infection usually does not occur and this explains the absence of beneficial effects from antibiotics. The indicated frequency of etiologic agents shown in Table 1 is drawn from the review by Chanock and Parrott.[3] It is clear that each clinical syndrome may be caused by many different agents. Rhinoviruses are a chief cause of acute rhinitis in adults but in infants and children many viruses cause the common cold syndrome, i.e., sneezing, rhinorrhea, anorexia, muscular aches, low grade fever, injected eardrums, thicker to purulent secretions in 2 to 3 days, lasting a total of 6 to 10 days. Herpangina in outbreaks in the summer is caused largely by Coxsackie A viruses but it may be simuated by herpes simplex virus. Attacks of pharyngoconjunctival fever are caused chiefly by adenovirus types 3, 7, and 14, and more endemically in young children by types 1, 2, and 5. Infectious mononucleosis is a laboratory-clinical syndrome of nonbacterial etiology for which no agent has been identified but which shares many clinical features with other upper respiratory infections and may simulate diphtheria and streptococcal infection. Herpes simplex virus, in addition to all the other syndromes it may induce, can also cause acute undifferentiated upper respiratory disease, bronchitis, and sore throat.[13, 14] Laboratory tests indicate that these symptoms may be caused by both primary and recurrent herpes infection.

In a three-year study of acute respiratory infections in children up to 16 years living at home, the British Medical Research Council found the age distribution shown in Table 2.[20] Respiratory syncytial virus was obtained almost entirely from children under age 6, and 60 per cent from those under 1 year of age. Parainfluenza viruses were isolated from infants under 1 year of age but mainly from children between 1 and 6 years with significant numbers up through 10. Adenoviruses and enteroviruses were most frequent in those between ages 1 and 10. Herpes simplex and rhinoviruses were found in almost equal frequency in all age groups, as was influenza virus. Herpes virus, influenza viruses, and beta hemolytic streptococci were rarely isolated from infants under 1 year of age. Streptococci were isolated in 4 per cent of children 1 to 5 years of age, in 14 per cent of those 6 to 10, and in 12 per cent of those

11 to 16 years of age. It was a striking finding that almost all cases of infection with beta hemolytic streptococci had been diagnosed clinically as sore throat.

Significant diagnostic procedures to rule out infections that require specific therapy include: immunization history for diphtheria and pertussis, white cell count and differential, and a throat culture to rule out beta hemolytic streptococci. Many beta hemolytic streptococcal infections in children present as tonsillitis, and pain is a prominent symptom. A throat culture is necessary to establish this diagnosis and then the patient should be treated for ten days with penicillin.[15] Therapy of the viral infections includes the use of nasal decongestants, antihistamines, acetylsalicylic acid, and other supportive measures.[16]

Bronchitis (Laryngotracheobronchitis, Acute Bronchitis)

In infants the classic symptoms of infection are fever, brassy cough, hoarseness, stridor, sore throat, nasal discharge, and malaise. Physical signs consist of slight injection of the throat with no exudate and are continuous in contrast to spasmodic croup. Laryngotracheobronchitis is a more severe edema of the larynx and subglottic mucosa, with obstruction, toxemia, chest retraction, fever, and production of thick secretions in the bronchi and trachea. Laboratory tests are not diagnostic. Bacterial secondary infection is usually not present, but in severe disease, broad spectrum antibiotics should be given, together with all supportive measures, including tracheotomy if the patient's airway is not open enough to permit him to sleep when placed in an oxygen tent.

Childhood respiratory infections involving the larynx, trachea, or bronchi are caused chiefly by parainfluenza virus type 3, respiratory syncytial virus, and in some cases adenoviruses and rhinoviruses. Influenza and measles viruses may be a significant cause in epidemic years. It is important to distinguish infections due to Haemophilus influenza with epiglottitis from diphtheria so that appropriate antibiotics and management can be instituted. Group A streptococci, pneumococci, and staphylococci are of doubtful significance in this syndrome.

Croup (Spasmodic Croup)

Croup occurs typically in children one to four years of age, rarely after age five. Attacks usually come at night following a mild upper respiratory infection and occur repeatedly in certain children and in certain families. The child awakens with a barking cough, dyspnea, and apprehension, clutches his throat, and uses accessory respiratory muscles. The voice is hoarse, and there is slight or no fever. There is respiratory retraction of the soft tissues in the suprasternal and supraclavicular areas. The attack passes off in a few hours, perhaps to return again the next night. Attacks are shortened by inhalation of moist air, syrup of ipecac to induce vomiting, and sedatives to reduce apprehension.

The parainfluenza viruses, particularly types 1 and 2, are the most important agents causing the croup syndrome.[13, 17] These viruses have been isolated or implicated serologically in 28 to 30 per cent of cases. Respiratory syncytial virus, adenovirus, and, in epidemic years, influenza A or B may also cause this condition, and mixed infection as shown by a rise in antibody for two or more viruses has been observed in 8.2 per cent of cases.

Bronchiolitis

This disease is seen in the first two years of life, but particularly in the first six months, and may be fatal. It is characterized by low or moderate fever, limited laryngeal involvement, dry cough, increasing dyspnea, emphysema, rapid shallow respirations with an expiratory grunt, and suprasternal as well as subcostal retraction on inspiration. Inability to sleep, pallor, and cyanosis indicate decompensated ventilation. The chest is hyperresonant; fine expiratory rales or sibilant, musical sounds are common. Symptoms frequently persist for seven to ten days or longer. Sporadic cases occur through the year but tend to group in sharp outbreaks in the winter or spring.

Respiration syncytial virus is the most important cause of bronchiolitis as well as of all serious lower respiratory tract infections in infants under six months of age. It was detected in 26 to 30 per cent of bronchiolitis cases by virus isolation or serology.[5] Parainfluenza virus type 3, adenoviruses, and mixed virus infection account for another 15 to 20 per cent of cases. Diagnosis is made on clinical examination and is relatively easy in epidemic periods, but one must consider other conditions such as foreign body, diphtheria, asthmatic bronchitis, miliary tuberculosis, pertussis, and mucoviscidosis. Treatment is symptomatic – cold vapor, oxygen, hydration, and nourishment. Respiratory assistance may be required in a few cases. Antibiotics are not helpful and secondary bacterial infection seldom occurs. Corticosteroids are not proved to be beneficial. Hospitalized patients should be isolated from other small infants.

Pneumonia

Pneumonia is one of the most serious infections in infancy and childhood and the clinical picture and course varies considerably with the etiology. All classes of microorganisms can cause pneumonia, including bacteria, viruses, rickettsiae, mycoplasma, fungi, and protozoa, and in addition aspiration or inhalation of toxic substances in young infants. The diagnosis is made by physical examination and x-ray but guidance for an etiologic diagnosis is gained by a careful history, the season of the year, and the prevalence of epidemic or endemic disease in the community. Bacteria that cause a small percentage of pneumonia in infants and children include pneumococci and Haemophilus influenzae, and in newborns, staphylococcus, Friedländer's bacillus, and gram-negative rods. Viruses are the chief cause of pneumonia in infants and children and the recently discovered viruses account for at least half of the cases for which an etiology can be proved. The most significant virus is respiratory syncytial virus, followed closely by adenoviruses. Also significant are parainfluenza viruses, particularly type 3, influenza A and B in epidemic years, rhinoviruses, Mycoplasma pneumoniae, and Coxsackie B viruses. Other causes less commonly seen in childhood include psittacosis, lymphocytic choriomeningitis, Q fever, histoplasmosis, coccidioidomycosis, and tuberculosis. The clinical course, diagnosis, and treatment vary with the etiology and will not be discussed in detail here.

CLINICAL DIAGNOSIS OF RESPIRATORY DISEASE

The British study of viral disease[20] provides a comparison of clinical diagnosis with viral etiology, as determined by laboratory tests, in patients seen in a home environment (Table 3). All agents were isolated from patients with "common cold" and "feverish cold," but rhinoviruses and adenoviruses predominated. Influenza virus was isolated in over half the patients diagnosed as having "influenza." "Sore throat" was associated with beta hemolytic streptococci, enteroviruses, and adenoviruses. The most frequent isolate in croup was parainfluenza virus; in bronchiolitis and pneumonia it was respiratory syncytial virus. One of the striking observations in this study and in the study by Chanock and Parrott[3] was the association of respiratory syncytial virus with severe respiratory infection in the first year of life and particularly in infants under six months of age.

Respiratory Syncytial Virus

In tissue culture this virus causes formation of giant cells, or syncytia, from which its name is derived. There is one serologic type. It is highly infectious and yearly epidemics occur in young infants. Attack rates are nearly 100 per cent in susceptible children. The incubation period in children is about four days. Milder disease is caused in older children and adults.

Most adults have neutralizing antibody for respiratory syncytial virus, and newborns have transplacental antibody but they still contract infection, as do adults when reexposed. Experimental inactivated vaccines are being evaluated but efficacy for disease prevention remains to be established.[21]

Parainfluenza Viruses

Parainfluenza viruses grow in tissue culture without visible cytopathic effects. Their presence is detected by flooding the culture with guinea pig erythrocytes which agglutinate about virus infected cells (hemadsorption). There are four antigenic types. These viruses share common antigens with mumps virus and Newcastle disease virus. By the age of eight years a majority of children have antibody to types 1 and 3. Reinfection occurs and causes milder disease in older children. The incubation period is five to six days. The parainfluenza viruses, particularly type 1, are the most important causes of the croup syndrome, but they also cause bronchiolitis, bronchitis, pneumonia, and upper respiratory disease. Parainfluenza virus, type 3, like respiratory syncytial virus, produces a large share of illness in very early infancy and can infect and produce disease in the presence of neutralizing antibody. Like respiratory syncytial and influenza A and B viruses, it spreads very rapidly to susceptible persons. Experimental vaccines are under study and laboratory studies look promising but clinical proof of efficacy is wanting.[21]

Primary Atypical Pneumonia, Eaton's Agent Pneumonia, Virus Pneumonia

Mycoplasma pneumoniae causes the highest incidence of pneumonia in children 5 to 14 years of age; infection in younger children causes a milder disease.[12] The percentage of infected persons who develop pneumonia has been estimated from 3 to 30 per cent in different studies.[3, 23] The incubation period is 9 to 12 days in volunteers but three weeks in carefully observed family contact cases.[12] Usual symptoms include cough, headache, fever, sore throat, and malaise, which may progress to pneumonia in a small percentage. Fine inspiratory rales are

Table 3. *Isolations from Patients with Various Illnesses*[*]

CLINICAL DIAGNOSIS	TOTAL	INFLUENZA	PARA-INFLUENZA	RS	ADENOVIRUS	HERPES SIMPLEX	ENTEROVIRUS	RHINOVIRUS	β-HEMOLYTIC STREPTOCOCCI
Common cold	437	1	*15*	8	8	6	13	28	11
Feverish cold	341	8	13	6	*26*	1	14	20	7
Influenza	144	*23*	2	1	3	1	5	4	4
Sore throat	376	1	4	1	*31*	7	32	8	*90*
Croup	127	2	*11*	3	4	1	3	6	6
Bronchitis	179	0	7	8	8	2	8	4	3
Bronchiolitis	46	0	1	*10*	1	0	4	3	0
Pneumonia	103	0	4	*12*	2	5	4	2	2
Otitis media	42	0	1	1	0	1	3	0	1
Other	93	0	3	0	3	5	7	3	4

[*] Modified from Tyrrell, D. A. J., et al.: A collaborative study of the etiology of acute respiratory infections in Britain. 1961–4. Brit. Med. J. 2:319, 1965.

RS, respiratory syncytial virus.

common but may be negative in hilar involvement. In pneumonia the white cell count is frequently 10,000 to 15,000 per cu. mm. The disease persists for one to two weeks. Otitis media occurs but its frequency has not been established. Agglutinins for Streptococcus MG develop late in the illness. Mycoplasma pneumoniae can be cultured on artificial media from sputum and there is a rising titer of cold agglutinins for human type O red cells. Specific serologic tests for the organism include fluorescent antibody test, complement fixation, and indirect hemagglutination tests for M. pneumoniae. In young infants pneumonia due to respiratory syncytial virus, parainfluenza virus, adenoviruses, and influenza virus resembles M. pneumoniae infection. Treatment with tetracycline derivatives is effective in mycoplasmal pneumonia. Formalin-killed vaccines of organisms grown in artificial media are under investigation.

Rhinovirus

Some strains grow in monkey cells (M strains), and others grow in human cells (H strains) at temperatures below the optimum for most other viruses. Sixty strains have been identified and many more may be discovered. Young children are relatively free of antibody for rhinovirus but 50 per cent of adults have detectable antibody. The incubation period in volunteer studies is 1 to 2 days. Infected adults have mostly acute rhinitis, but in children at least half of those infected develop bronchitis, bronchiolitis, or bronchopneumonia, which is generally milder than the disease caused by respiratory syncytial virus. Development of vaccines is hampered by the large number of antigenic types.

Adenoviruses

There are 31 types identified by the neutralization test. All share a common complement fixation antigen. Numerous clinical syndromes have been described and will not be discussed in detail here. Types 3, 7, 12, 18, and 31 cause sarcomas when injected into newborn hamsters and this raises a problem in connection with development of killed and living vaccines.[3, 21] Experimental killed vaccines against types 3, 4, and 7 have protected military recruits. Types 1, 2, 5, and 6, of greater importance in childhood infection, are poor antigens. Type 4 adenovirus seems to form hybrids with SV-40 virus, which is oncogenic for hamsters. Living vaccines fed orally seem to hold promise.[22] An enteric infection is established that stimulates antibody production and is not infectious to contacts.

Influenza Viruses

Influenza viruses type A and B cause highly infectious respiratory disease characterized by fever, myalgia, cough, headache, and prostration. The incubation period is 1 to 2 days. Dyspnea, retraction, or cyanosis indicates pneumonic involvement. Major epidemics of type A occur every 2 to 4 years and antigenic variants have appeared at intervals of roughly ten years. Type B recurs at intervals of 4 to 6 years and antigenic variants appear more slowly. The disease is usually mild in healthy children but complications and death may occur in debilitated patients. Secondary bacterial infection of sinuses, ear, bronchi, and lungs may occur. Staphylococcal pneumonia caused by antibiotic-resistant strains may be a serious problem. Mortality is highest in persons of any age with preexisting pulmonary or cardiac disease.

Laboratory confirmation can be obtained by virus isolation and specific serologic tests, on acute and convalescent sera. Influenza virus presents more explosive epidemics, more rapid onset, with severe systemic symptoms, and shorter course than most other viral respiratory diseases. Antibiotics are not helpful in uncomplicated disease but should be used for bacterial complications. A new synthetic compound, amantadine hydrochloride (Symmetrel) is being marketed as a prophylactic for influenza A_2 (Asian) virus infection, but its eventual usefulness is not yet established in clinical practice. The recommended oral dose for adults is 200 mg. per day for as long as exposure exists. In limited clinical trials the drug reduced influenza A_2 infection up to 50 per cent in volunteers. Central nervous system reactions occur, especially in geriatric patients, and with a dose of 300 to 400 mg. per day side effects are noted in many patients. The drug has no direct toxic effect on influenza virus and seems to act by blocking adsorption of the virus to the cell membranes. It is not effective against influenza B virus. Until further studies and observations are available it cannot be recommended for use in the pediatric age group.

For prevention, formalized vaccine is effective in military personnel and in adults. Routine immunization is not recommended for infants and children because severe febrile reactions to the vaccine may be observed, and the disease is generally mild in children. For those at special risk the vaccine should be used in smaller doses and repeated yearly in the fall.

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Current Status of National Immunization Programs

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Currently in the United States immunization is used as a *routine* primary preventive measure against relatively few diseases – smallpox, diphtheria, pertussis, tetanus, poliomyelitis, and measles. But there is more than this to immunization practices in this country.

United States citizens who are travelers to foreign countries may require immunization against such diseases as yellow fever, cholera, plague, epidemic typhus, and typhoid and paratyphoid fevers, in addition.

Rabies vaccine ordinarily is used in man only after known or suspected exposure to the virus, although preexposure prophylactic rabies vaccination may be recommended for persons at high risk, such as veterinarians, laboratory workers, and animal handlers.

Vaccination against influenza generally is recommended for the elderly and for persons of all ages who are suffering from chronic debilitating illnesses.

Under special circumstances involving high risk of exposure, selected population groups or individuals may be immunized against specific diseases including tuberculosis, anthrax, Rocky Mountain spotted fever, and certain of the arthropod-borne viral diseases.

Passive immunization may be employed on a selective basis with immune serum globulin against measles and infectious hepatitis and with special immune serum globulins against measles, mumps, pertussis, tetanus, vaccinia, and smallpox.

This is a substantial array of immunization activities, many of which are used widely throughout the country by health departments and by private practitioners. Which of them, then, might appropriately be considered within the term, *national* immunization programs?

For purposes of this discussion, I propose to limit consideration to those activities that are authorized and supported by specific federal legislation – namely, the Vaccination Assistance Act of 1962, as amended. This is a relatively uncomplicated law that has made possible a coordinated nationwide approach resulting in substantial improvement of the immune status of our population, particularly the younger segment.

What are the provisions of this legislation? The original act in 1962 authorized project grants by the Public Health Service for a three year period to assist states and communities in carrying out intensive vaccination programs against four diseases – poliomyelitis, diphtheria, pertussis, and tetanus. An amendment in 1965 extended the program for three additional years and authorized the Surgeon General to include measles and any other infectious diseases of major public health importance for which a vaccine or other preventive agent might become available.

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Grant funds provided under this authority can be used for purchase of vaccines for preschool-age children and salaries and related expenses of additional state and local health personnel needed for planning, organizational and promotional activities, studies and demonstrations, and additional epidemiologic and laboratory surveillance. Vaccines or personnel or both instead of cash can be provided by the Public Health Service upon request by the state or local health agency. No matching funds as such are required of the grantee; however, states and communities, for their part, are responsible for supporting all other elements of the intensive program, including the purchase of vaccines for persons other than preschool-age children, and the services of physicians, nurses, and other health personnel required in the conduct of public programs.

Although designed particularly to support intensive, time-limited campaigns to immunize the backlog of susceptibles in the communities, the act also provides for the development of on-going programs for the immunization of newborns and for the maintenance of immunity levels in the remainder of the population. This is one of the attractive features of the program—that it is not just a one-shot crash effort but rather that it provides also the mechanism for developing an activity that is to continue even after federal support may be withdrawn.

The act authorized grant funding levels of $14 million the first year and $11 million for each subsequent year. Actual appropriations, however, have been less than the authorized ceilings—$8.7 million in fiscal year 1963, $10.2 million in fiscal year 1964, $8.0 million in fiscal year 1965 and again in fiscal year 1966, and a requested $9.1 million in the President's budget for fiscal year 1967.

The program, which is administered by the Communicable Disease Center in Atlanta, received its first appropriation in May 1963. What activities have been carried on in the four years that the program has been in operation? How close have we come to the goal of immunization of virtually all susceptible preschool children and most school children and adults against the five diseases? And what has happened to the morbidity and mortality caused by these diseases?

Since this is a grant program, some indication of program activity can be gained by looking at the grant awards. Project grants are of two types—those that help support statewide programs and those that help support local programs, i.e., city or county. At the present time grant awards go into 103 immunization projects, of which 42 are statewide and 61 are local. There are only two states in which there is no project at this time and only one state that has never had a project of either type. The 103 active projects cover areas which include 82 per cent of the total population of the United States, Puerto Rico, and the Virgin Islands.

Primary emphasis is placed on the immunization of preschool children. In addition, each project is developing a system based upon follow-up of birth certificates to assure that a satisfactory immunization status for all newborns is achieved. Approximately two-thirds of the current projects have fully operable systems; the remainder are in the developmental stage. Methods used range from hand-manipulated data cards to highly refined computer operations in the larger projects. Parenthetically, the point can be made here that although this is truly a nationwide program, the activities within individual projects do not have to fit a stereotyped pattern, but rather are developed around the needs, resources, capabilities, and desires of the various state and local health agencies.

Using vaccines obtained from sources other than through the Vaccination Assistance Act, many projects have promoted increased immunizations for school age children. A number of projects also have developed on-going relationships with industry and labor, with hospitals, and with other organizations to assure continuing immunization programs for adults.

Along with administering the grant program, the Communicable Disease Center through its various branches provides support and assistance to the projects in a variety of ways. These include placing increased emphasis on epidemiologic surveillance of the five diseases, on the conduct of immunologic surveys and the evaluation of vaccines, and on the investigation and surveillance of other diseases for which immunizing agents are expected to be developed. Support for laboratory activities directly related to immunization programs has been provided to 13 statewide projects and five local projects in large metropolitan areas.

Various types of promotional materials for immunization campaigns have been developed in prototype form at the Communicable Disease Center for distribution to the state and local projects. These include printed materials, exhibits, recorded and taped radio announcements, filmed television announcements, and booklets on procedures for carrying on intensive community campaigns. Two films are being released this fall–one of 13 minutes on measles, and another of 25 minutes on tetanus.

Through the establishment of a clearing house in Atlanta, information regarding activities and materials of demonstrated effectiveness in given individual projects are made available to all state and local health departments participating in the national program.

A cooperative project with the Veterans Administration was undertaken in which more than ten million veterans and their families were provided information on the need for immunization and were furnished immunization record cards.

Heavy emphasis has been placed on training and education activities, directed toward state and local health personnel and the medical profession. Courses and seminars have been presented throughout the country on survey methods, vaccine administration, including the use of the hypospray jet guns, organization and management skills, and immunization in general. It may be of interest to note that, at a recent meeting, the Board of Trustees of the American Medical Association commended the Communicable Disease Center on the services it provides for postgraduate symposia on immunizations, and recommended that local medical societies give consideration to requesting these services for the purpose of improving the immunity status of their communities.

Professional and authoritative advice is given to the program on a continuing basis by the Surgeon General's Advisory Committee on Immunization Practices, a group comprised of outstanding consultants in the field.

As authorized by the Vaccination Assistance Act, the Communicable Disease Center is providing 89 persons instead of cash at the request of state and local health departments. Included in this total are 23 Epidemic Intelligence Service Medical Officers engaged in surveillance activities for the five diseases covered by the program and 66 public health advisors assigned to assist in program implementation and execution. Of interest is the fact that approximately 1300 persons employed by state and local health departments are engaged in implementing the intent of the act–including physicians, nurses, program representatives, health educators, statisticians, community health aides, and clerks.

Although these program activities are important, to be sure, in getting the job done, they are just that–program activities–and are not necessarily true measures of accomplishment of the task at hand, namely, getting vaccines into people. There are data available, however, that do provide some indication of the progress achieved in this regard.

Through an agreement with the Public Health Service, since 1962 the Bureau of the Census has conducted in September of each year a National Immunization Survey. The information so obtained has great applicability for evaluation of progress and for basing decisions on future courses of action. Comparison of data from the 1962 and 1965 surveys does show significant progress in getting target groups immunized.

For example, in the one- through four-year age group there was a 5.9 per cent increase (from 68 per cent in 1962 to 73.9 per cent in 1965) in the number of children who had received a basic series of diphtheria-tetanus-pertussis inoculations. This reflects protection for about one million more preschool children than three years previously.

In the five- through nine-year age group, three million more children had received four or more doses of DTP vaccine in 1965 than in 1962. This increase from 52 per cent to 66 per cent immunized is of particular importance since it reflects a significant increase in school immunization activities even though the vaccines for these children are not provided under the federal legislation.

Survey data revealed also that more children are receiving immunizations prior to their first birthday. Thus, approximately one-quarter million more children under one year of age had received one or more doses of DTP vaccine in 1965 than in 1962—an increase from 57 per cent to 63 per cent.

A striking gain in immunization protection against poliomyelitis has occurred with the advent of the oral vaccine in 1962. Between September 1962 and September 1965 the percentage of one- through four-year-old children receiving all three types rose from 6 to 49—representing over seven million more preschoolers immunized.

Exactly comparable data are not available for measles vaccinations. This vaccine was licensed in March 1963 and has been included as one of the vaccines in the national immunization program only within the past year, following the 1965 amendment of the Vaccination Assistance Act. Since its licensure, it is estimated that approximately 15 million doses of live attenuated measles virus vaccine have been distributed for use in the United States. It is further estimated that the number of susceptible children has been reduced from 20 million to 12 million.

Program activities and numbers of persons immunized are useful indices of effort and accomplishment. However, the ultimate test of success of an immunization program, be it local, statewide, or national in scope, is in its effect on the morbidity and mortality caused by the diseases toward which the program is aimed.

Here I must state that it is impossible to define clearly the impact of the national immunization program on the five diseases. The program has been additive to, and has provided a mechanism for augmentation of, immunization efforts that have been practiced to a greater or less degree for over four decades in many state and local health departments and by private physicians throughout the country. The program is aimed at specific target population groups most in need of immunization, and we are confident that it has had positive effects even though we may not be able to express those effects precisely in quantitative terms.

Let us consider briefly the changes in disease patterns over the past ten years. In 1955 there were nearly 14,000 cases of paralytic poliomyelitis reported in the United States; in 1965, there were 61. The inactivated virus vaccine came into public use in 1955, followed by the attenuated oral vaccine in 1962.

Reported cases of diphtheria totaled nearly 2000 in 1955, but only 164 in 1965, with an increased rate of decline from 1964 to 1965 that continued into the first 36 weeks of 1966.

Pertussis dropped from over 62,000 reported cases in 1955 to something less than 10,000 in 1965. However, this disease is poorly reported and is often inaccurately diagnosed; the trend, therefore, must be interpreted with some caution.

Reported cases of measles fluctuated around 450,000 to 500,000 cases per year until 1964, but showed a substantial drop to 265,000 in 1965, with the decline appearing to continue in 1966. This drop is directly associated with the advent of the measles vaccine.

Of the five diseases, tetanus has shown the least change over the ten year period despite extensive immunization of children. Over half of all cases reported in recent years occurred among adults.

Substantial progress has been made. We have reached the point at which one can say that a case of poliomyelitis or diphtheria in a child should not have occurred. By 1970, it has been predicted, the same can be said of measles.

But there are still problems with which we must deal. There are still pockets of unimmunized people, especially in the lower socioeconomic groups. These people are often hard to reach with conventional programs and are often equally hard to motivate to seek the protection afforded by immunization. For these reasons, immunization project personnel have developed and adopted new approaches and techniques designed to reach and to motivate these unprotected individuals and families. In some instances these approaches have been successful; in others, the solutions to hard-core situations are still to be found.

In summary, a national immunization program, authorized and supported under federal legislation, and directed toward poliomyelitis, diphtheria, tetanus, pertussis, and measles has been underway since May 1963. The program is truly nationwide in scope and has enabled the participating state and local health agencies to substantially augment their own immunization efforts. Further, it has been characterized by a high degree of cooperation and participation of local civic and volunteer organizations, medical societies, and individual practicing physicians. Although creditable and measurable progress has been made, much remains to be done before the eradication of some of the diseases and the achievable reduction of others are accomplished.

Bureau of State Services
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Community Organization for Immunization Programs

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In discussing community organization for immunization programs I have no intention of outlining a blueprint for a mass immunization campaign. This blueprint was written most effectively in a manual for the national field trials of poliomyelitis vaccine.[2] With slight modifications it can be used today to meet most situations. Rather, I wish to direct attention to points of view that apply to continuing immunization programs, mass campaigns, and programs concerned with the trial or introduction of a new vaccine. Above all, I want to focus on the nonimmunized socially deprived members of society among whom we have seen outbreak after outbreak of truly preventable diseases. Foresight and action are necessary so that these episodes may disappear completely.

Objective

Our objective in medicine and public health is to promote immunization as a cultural pattern. All segments of our society must recognize and act upon the need to immunize children in the first year of life and to accept immunization in preparation for potential or anticipated exposure to infection. Parenthetically, immunization activities must be incorporated into on-going programs related to maternal and child health, pediatric care, and school health services.

In time we should achieve a complete immunization of practically all persons in this country against diphtheria, pertussis, tetanus, measles, poliomyelitis, and smallpox, and also against rubella and mumps. We trust that, as technical discoveries are made, other antigens will be developed that may be included and thus the toll of disability and death may be further reduced.

In consideration of our position in the world, not only must we accomplish our objective, but demonstrate by example that major causes of disability and death can be controlled. We must demonstrate also that we have learned to cope effectively with the educational, social, economic, and cultural factors that impede or delay immunization and disease control in other countries of this hemisphere and the world.

Responsibility

If we are to achieve our objective in the control of disability and death via immunization, it is clearly necessary that responsibility for decision and action be defined.

Although I recognize that public health services may be rendered by voluntary agencies, the primary responsibility for the health of the public is vested in government. Traditionally, government has been called upon to "control communicable disease."

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In their legislative authorizations, all levels of government are empowered to receive reports of disease, investigate causes, and apply measures of prevention and control. To these ends, there is a mandate to government to assume leadership and act in behalf of the total public welfare. Governments have the legal, administrative, fiscal, and technical means available to act. Unfortunately some governments move with more reluctance than enthusiasm.

The practitioners of medicine in this country represent a tremendous force for positive achievement. These doctors and their various organizations, because of their massive influence on the populace, represent a huge potential to stimulate immunization activity. In the recent past, because of changing social climate, the medical profession has been subjected to close scrutiny with resultant tarnishing of its previously bright altruistic image. Good health has not only become a right of citizens but is demanded by them. Immunization activities are a fertile area in which the practitioner may simultaneously discharge his accepted obligation to improve the health of man, satisfy the public demand of the right to good health, and reinstate the image of the physician.

Essentially, the medical practitioner is sincerely and deeply individualistic. His practice is his life. His concerns, for the most part, are oriented toward the individual patient. He frequently views problems and programs only through the perspective of his office. He may be unaware of what is happening among persons he never sees, and, in a collective sense, a county medical society may fail to perceive what is happening outside the environment of their collective practices. For these reasons, there is an incumbent responsibility upon government and the practitioners of medicine to unite their interest in immunization, to examine its current status and to plan and execute effective programs.

As an example, I remind you that 93 cases of paralytic poliomyelitis were reported in 1966 in the United States. Seventy-two were from Texas, 67 among preschool children, principally of Latin-American origin.[6] A health department and a medical society viewing such evidence have a joint obligation to do something about it. This example demonstrates the need for close cooperation between public health practitioners and the medical profession.

We have the material and the method to prevent outbreaks of poliomyelitis. Their occurrence signals a breakdown in the area of administration, planning, communication, and social perspective, which cooperative action can overcome.

Surveillance

Accepting the concept that the health department and medical society are jointly responsible for immunization in a community, we see that there is an immediate need for organized information that can be evaluated and used to determine a course of community action. This need involves the development of a system of surveillance. By surveillance is meant the continuous study and evaluation of the incidence of a certain disease or diseases, using all available sources of morbidity, mortality, and laboratory data. This definition can be expanded to include data collected on the immunization status of a population and the volume of antigen produced, distributed, and used.

The health department is responsible for the collection of morbidity and mortality data and, in many states, for the collection of laboratory data indicative of communicable disease. This data, organized and evaluated, indicates areas where disease is occurring and stimulates investigation of the cause. In the 1958 poliomyelitis outbreak in New Jersey, the poliomyelitis virus sought out, infected, and thus revealed nonimmune persons in Jersey City and Newark. A rapid immunization survey revealed that complete immunization in the preschool age group did not exceed 16.3 per cent.[1] The obvious decision in the face of such evidence was to initiate and pursue aggressively a continuing immunization program.

In the same year, Serfling developed a more refined technique that revealed the social and economic factors associated with levels of immunization; specifically, the importance of the nonimmune status of low socioeconomic groups.[3]

Today, with the use of sampling techniques, immunization surveillance makes it possible to seek out low levels of immunization in the community. Armed with this information, a health department and a medical society can marshal their combined resources, plan and conduct a program, and avert the threat of disease and disability.

Planning

The health officer faced with surveillance data indicating need has several avenues to pursue, simultaneously.

The local chief executive and governing body require notification and orientation concerning the need for community action. At the same time, the health officer must notify the local medical society and obtain the support of its members. When these actions have been accomplished, there is need for a planning meeting, which serves at least two purposes:

1. To inform key representatives of the professional, social, educational, and economic groups of the community concerning the nature of the need for immunization.
2. To obtain necessary support for an immunization plan. Among the groups to be represented are: medical society, pediatric society, nursing organizations, educators, Parent-Teachers Association, minority and special interest groups and essential governmental agencies.

This type of planning meeting taps the resources of the community and provides the nucleus for action.

Coordination

The early phases of a program can be handled by an ad hoc committee, but there soon comes a time when coordination of effort is a must.

Delegation of responsibility for the program must carry with it the authority to decide and act. Thus, the choice of a coordinator is a most important act. The areas in which coordination is necessary include: funding, supplies, equipment, professional and volunteer personnel, clinic sites, storage, and transportation. In these areas, it is desirable and necessary to work out and spell out the details to be performed by various people and groups. Careful attention to detail and avoidance of overlapping activity prevents confusion, chaos, and catastrophe.

The area in which coordination is most essential is in relations with power groups and communications.

The success of a program depends upon the participation and good will of many groups of people, professional, social, educational, economic, political, majority, and minority. These groups have varied attitudes and aspirations, which motivate them to serve. They serve in several ways as a source of manpower, as an audience to be taught, and as a force that will in turn disseminate information and enthusiasm among their peers and those who share their interests.

Ample use should be made of organized groups without regard to their conflicts or attitudes toward the community at large. In the depths of an old city, people involved in the organization of a Sabin Oral Sunday turned to the neighborhood band of juvenile delinquents in one neighborhood and to narcotic addicts in another, to serve as the communication link with the people of the neighborhoods. These youngsters and people were pleased to render a socially acceptable service.

Power groups must be considered as human beings with an intense desire for recognition. For this reason, their ideas should be accepted, weighed with them, and used, if practical. Their initiative and accomplishments should be clearly stated and commended both during and after a program. Too often we forget to thank the field soldiers who make success possible. Too often the health department or medical society gets the lion's share of the acclaim. The blame we should absorb; the acclaim we should spread to less visible people, who make success possible.

In the area of communication, there should be one spokesman for the program, authorized to deal with the press, radio, and television, and to manage printed material for widespread dissemination. He should be assisted by professional and technical personnel. It goes without saying that accuracy, clarity, brevity, and simplicity are features to be incorporated in communications media.

In programs of substantial size, there are often times when unanimity of expression or purpose may be lost. All efforts must be expended to preserve unanimity. Controversy begets confusion, diminishes confidence, and melts support. It is heartbreaking to see a healthy program wilt and die because of actual or implied controversy.

Levels of Public Understanding

The development of a sound community education program to create and enhance public understanding of immunization is a most important effort.

Immunization programs are conducted with the support and understanding of community groups and individuals and the acceptance and understanding of the majority of the community. The inertia we see in communities is not disinterest or lack of concern, but rather a matter of lack of understanding.

In a recently completed survey in which questions were asked about the reporting of specific diseases, a surprisingly large number of physicians were not aware of current facts of disease incidence. If this lack of understanding can occur among physicians, how much more likely is a lack of understanding of immunization among the nonprofessional, the poorly educated, and the illiterate.

In approaching public understanding, the first factor to be explained is the need for the program. People will want to be immunized if they understand the benefits they will receive. For a program to be successful, the people must act from motives of self-interest.

The private physician is essential in creating a desire for immunization in the minds of the great majority of our people. All physicians must be aware of and express the need for immunization to their patients. General practitioners, pediatricians, surgeons, obstetricians, and members of hospital staffs all have an obligation to stress the benefits of immunization to the patients they see. Consider the volume of service and the extent of immunity developed if each practitioner routinely questioned his patients concerning their immunization status and immunized them when it was indicated. I stress the role of the physician in his practice because his influence is vital to the attainment of public understanding and public confidence. The information he imparts about the need and benefits of immunization is relayed from his patient to other persons through existing social channels.

We must admit, frankly, that there is fear of immunization in the hearts of many patients. They fear the discomfort and some are concerned about the pain of injection. To offset this, it is essential that the physician emphasize the protection and benefits to be obtained by immunization.

The explanation of need to persons who are not beneficiaries of private care is another matter. As a general rule, all groups affected by a program should have a part in shaping and directing it for through participation they learn its purpose, its meaning and its benefits to them.

To make this point more emphatic, let me pose several questions:

How often has your medical society or hospital staff consulted with the socially deprived of your community about the availability and character of clinic services?

How often, when we think of immunization programs, do we take the attitude: let's get them in, let's line them up, let's get it over with. I have done it and I am sure that others have done it the same way.

I question whether this is the effective way to develop understanding and motivation for the immunization process.

We have an obligation to reach out to the deprived, to teach them, and to involve them in the learning, planning, and doing process. In so doing, we must learn to listen to them through a stethoscope of social and cultural conscience. Having listened, we should not then proceed to impose our will but employ the gentle art of reason, compromise, and persuasion. I will be the first to admit that we are not proficient and that we have much to learn in the process and that it will take patience and study.

The standard approaches of newspaper, radio, television, posters, and flyers, can be thrown into the effort, but the primary effect, particularly among low-income groups, may well be achieved by calculated gossip.

People like to talk, so person to person communication by public health nurses, sanitarians, bartenders, school teachers, local businessmen, and even the local juvenile delinquents and nondelinquents may serve to get the word around.

Recruitment and orientation of peer group workers is not easy to accomplish, particularly when multilingual and diverse social and cultural forces are present in the neighborhood. Just to find the right words frequently is a chore, and may be the difference between success and failure.

A film sponsored by the New Jersey State Department of Health and the Communicable Disease Center entitled "To Open a Door" will give you a sense of the environment, the characters, and the intimacy we feel is needed to reach groups who respond poorly to the usual approaches to public education.

I have stressed the factor of creating an understanding of the need for immunization. In dealing with community organization, we must, in addition, clearly describe where the immunization will be given, when it will be given, and how it will be given, in order that the potential recipients understand the process completely.

In considering how the service is rendered, these questions may be raised: Is there sincerity of purpose? Is there rapport? Is there friendliness? Is the recipient served with dignity?

Frequently, the socially deprived are herded, called sharply, and served impersonally. I recall talking to several members of a low socioeconomic group who had just been immunized in a clinic and I asked them what they thought; and to my chagrin, their response was "Oh, we were just shuffled off." These people measured the value of services rendered to them in proportion to the attitude expressed toward them.

Evaluation

The evaluation of a program should determine whether the immunization of susceptible groups was achieved. It should determine the effectiveness of the components of action contributing to the program. To accomplish an effective evaluation, one must have records and data with which to work. Forms and reports to be used, prepared, and submitted are an inevitable consequence; without them, statements of success are invalid. Careful reporting of disease subsequent to the program is also essential in completing the final evaluation.

Too often major efforts in public education, community organization, and action are completed without any final tally of the results of the effort. Too often the public, who through their participation have made a program a success, are unaware of the final results. We must remember to publicize properly the final outcome of every major undertaking in community organization.

Examples

I have discussed the familiar rules of community organization, and I now wish to provide a brief description of specific examples.

I must reiterate that study after study has shown that the socially deprived, the low-income groups of our society, are deficient in immunization status. In any one of our communities, we may overlook these people until an outbreak of disease suddenly appears. If we are to prevent disability and death due to tetanus, measles, diphtheria, polio, pertussis, and smallpox, we must dig into the difficult areas of our community and elicit the facts concerning immunization.

In March 1966, the New Jersey State Department of Health and Trenton City Health Department determined that in the low-income area of the city, approximately 52 per cent of the children under five years of age were susceptible to measles.

The Trenton Health Department in cooperation with the Community Action Program, which serves the economically deprived, is attacking this problem by reaching out to all deprived families. With the aid of the local schools, they hope to change susceptibility to immunity.

In November 1965, measles reached its highest peak in Dover, New Jersey, since 1959. On December 2, the Health Officer, with the assistance of local physicians, immunized 465 children, 80 per cent of those susceptible, in one parochial and three public elementary schools.[5] In 10 days the outbreak ceased abruptly. The epidemic curve suggests that the immunization program may have aborted the epidemic by reducing the number of susceptible children below the epidemic threshold.

This measles outbreak, the immunization program, and the attending publicity, which included national coverage by New York newspapers and television programs, had many effects that extended beyond the immunization of 465 children. Physicians in the area were suddenly besieged by parents with requests for immunization. The outflow of measles vaccine from the state's Biological Distributing Centers increased sixfold within a matter of a few days. Throughout the state, 34 small and large communities mobilized their resources and conducted campaigns that reached over 21,000 children.

We cannot talk about these benefits without being utterly frank. Sincere people, dedicated to their jobs, conceived this immunization program in haste. Many people who had specific interest in this undertaking were overlooked. This created unfavorable attitudes and impressions, particularly among the practicing physicians in the area. In this undertaking a prime rule was overlooked—involvement of the medical society.

Community action to determine susceptibility levels and to offset outbreak situations is now clearly indicated as sound medical and public health practice, and each community should now direct its attention to this valuable potential to eradicate the morbidity and disability of measles, poliomyelitis, and other diseases.

A survey of school children in socially deprived areas of Newark, New Jersey, in the spring of 1965 revealed over 7000 medically indigent children in need of complete poliomyelitis immunization. Parents and school and health authorities joined ranks to meet the challenge.

I would like to present two recommendations:

1. Local health departments in cooperation with appropriate county medical societies should determine the extent of incomplete immunization within their jurisdictions.

2. Local health departments and medical societies aided by organized community effort should conduct appropriate programs to assure complete immunization of the community, placing special emphasis upon the socially deprived.

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Immunization for Foreign Travel

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Never in the history of this country have more of its citizens had opportunities to travel abroad than at the present time. Whether on business, for pleasure, or upon order of the government, this international movement of people has reached astronomic numbers, and with our current political and economic interests abroad, this travel can only be expected to increase in the future. Most civil travel overseas is on a nonrepetitive basis to a specific country or geographic area, as, for example, the classic American tourist, or on a repetitive basis to specific cities on business. The vacationer abroad presents a somewhat different problem in immunization to his physician than does the regular business commuter, who, like a member of the Armed Services, can be prepared immunologically for his travel and maintained up-to-date for a specific area. For both types of traveler, the *International Regulations for Immunization* obtain. This communication reviews these immunization requirements and recommends certain guidelines for the traveler's physician.

Most Americans preparing for overseas travel present with a history of immunization to smallpox, diphtheria, pertussis, and tetanus. An appreciable number of the younger travelers have been immunized against polio viruses types I, II, and III. Almost all have a history of rubeola and chickenpox; younger children may have been immunized against measles. This is an excellent immunologic base from which to proceed. On the other hand, unless the traveler has had prior military service, he is unlikely to have been immunized against typhoid-paratyphoid, typhus, cholera, plague, rabies, and yellow fever. Immunizing agents are available for protection against each of these infections, yet it rarely is possible and seldom is practical to administer all of the additional vaccines. The physician, therefore, should know the relative risks his patient has of contracting these infections during travel and should be familiar with quarantine regulations governing mandatory immunization. The best published guide to these is the pamphlet *Immunization Information for International Travel*, published by the U.S. Public Health Service as document No. 384, available from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. A charge of 35 cents is made for this guide.

The mandatory immunizations are relatively few as contrasted to those merely recommended, and are summarized in Table 1.

YELLOW FEVER. Valid immunization for yellow fever within ten years is required for all those entering African countries, India, and certain countries in the interior of South America. It is also required for entry into the United States and Europe from areas in which yellow fever is endemic.

CHOLERA. Immunization against cholera within six months is required for entry into Africa, the countries of Southeast Asia, and currently the Indian subcontinent and the countries of the Middle East. It is also required for entry

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Table 1. *Mandatory Immunizations Required for Entry Into Foreign Countries, 1966*[*]

1. *Yellow fever* (within 10 years): West, central eastern and southern Africa, India, certain countries in interior of South America; most others, particularly those in yellow fever receptive areas, after travel in endemic areas.
2. *Cholera* (within 6 months): Africa, Southeast Asia, Indian subcontinent, Near and Middle East; most others after travel in endemic areas.
3. *Smallpox* (within 3 years): India; United States before reentry from anywhere abroad.

[*] For information on specific countries, see *Immunization Information for International Travel.* USPHS publication No. 384, Government Printing Office, Washington, D.C.

into almost every country from a cholera-endemic area. The initial course of immunization consists of two injections of vaccine subcutaneously at least four weeks apart. The dose is 0.5 and 1.0 ml., respectively; reimmunization (0.5 ml.) is required every six months.

SMALLPOX. A validated immunization against smallpox within the preceding three years is required for every traveler. Although only a few countries require this for entry, the United States insists upon it before reentry from abroad. This is a reasonable attitude, since only countries with similar regulations are consistently free of imported smallpox. The regulation provides for *no* exception. This poses problems for those who, by virtue of chronic skin disease or chronic blood dyscrasias, are susceptible to *eczema vaccinatum* or systemic vaccinia. Such persons may be successfully *revaccinated* after administration of vaccinia immune globulin in doses of 0.05 to 0.1 ml. per pound of body weight. *Primary vaccination* of such persons should be anticipated well before eventual travel since successful vaccination frequently requires four to six months. The ordinary procedure requires multiple injections of killed vaccinia virus, or, more recently, application of a special attenuated vaccinia virus. In either circumstance persons so immunized must be revaccinated in two to four months to determine the relative state of immunity. Consultation for these special cases is available from the Committee of American Red Cross Volunteer Consultants for the Distribution of Vaccinia Immune Globulin. The use of the further attenuated vaccinia virus, considered a biologic product in experimental evaluation, is currently controlled by Dr. Henry Kempe, Department of Pediatrics, University of Colorado Medical School, 4200 East Ninth Avenue, Denver, Colorado 80220.

Immunization against typhus, plague, poliomyelitis, tuberculosis, typhoid-paratyphoid, influenza, rabies, tetanus, diphtheria, and measles is recommended for travel to specific countries where these diseases are naturally common and widespread (Table 2). However, with the exception of entry into plague endemic foci in certain countries, they are *not usually required* by the quarantine services of the countries, or for reentry into the United States. Table 2 summarizes these suggested immunizations. The summary is modified from the immunizations required by the Department of Defense of its military and civilian personnel for foreign travel and incorporates the recommendations of Evans for the use of BCG.[*]

For the tourist or short-term business visitor anywhere abroad, immunization to assure some degree of immunity to typhoid-paratyphoid, diphtheria, tetanus, poliomyelitis, and measles is recommended as a basic series. Many previously immunized travelers require only booster injections of triple typhoid and diphtheria tetanus vaccines before departure. Children and young adults should be immunized against poliomyelitis and, if they are still susceptible, against measles as well. Primary or booster immunization against influenza using the commercially produced polyvalent vaccine is recommended prior to winter travel to Europe, and irrespective of the season for visitors to Asia and the Indian subcontinent. Finally, primary immunization against epidemic typhus is suggested for those persons whose travel will bring them in close contact with rural areas of Central and South America, Asia, the Near East, Africa, and the Indian subcontinent.

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[*] Evans, A. S.: The instant-distant infection. Am. M. Women's A. *21*:210, 1966.

The resident abroad should have the benefit of other prophylactic immunizations in addition to those recounted here. Plague vaccine is highly recommended for those whose foreign residence would take them to locally identifiable endemic areas in the interior of Brazil, Bolivia, Ecuador, Peru, and Venezuela in Latin America, the Congo, Kenya, Malagasy, South Africa, and Tanzania in Africa, Iran in the Near East, and India, and Burma, Cambodia, Indonesia, Laos, and Vietnam in Asia. The extent of natural activity of plague in these areas, as well as current information on other plague-endemic foci can be obtained from the Division of Foreign Quarantine, United States Public Health Service, Silver Spring, Maryland 20910. Commercially available plague vaccine is administered intramuscularly in two doses, 0.5 and 1.0 ml., the second given four or more weeks after the first. Those residing in a known plague-endemic focus should be reimmunized (dose, 0.5 ml.) every six months.

Similarly, persons residing in rural areas of Latin America, and of most Asian countries, particularly those engaged in programs for agricultural and economic development, should be immunized prophylactically against rabies. Three doses of duck embryo vaccine (1.0 ml. each) may be given intramuscularly at three to four month intervals, with a booster dose six to nine months after the basic series. Persons at extraordinarily high risk should be tested for neutralizing antibodies to rabies virus before booster immunization, and again two to three months later. Booster injections should be continued at three to four month intervals until neutralizing antibodies become detectable. For instructions on collection of sera and performance of this test, consultation with the state public health laboratory or veterinarian is suggested.

Table 2. *Recommended Immunizations for Foreign Travel, 1966**

TRAVELER CATEGORY AND IMMUNIZATION	EUROPE	CENTRAL, SOUTH AMERICA	ASIA	AUSTRALIA PACIFIC ISLANDS	NEAR EAST	AFRICA	INDIAN SUBCONTINENT
Short-term Visitors							
1. Typhoid-paratyphoid	X	X	X	X	X	X	X
2. Diphtheria-tetanus	X	X	X	X	X	X	X
3. Poliomyelitis	X	X	X	X	X	X	X
4. Measles	X	X	X	X	X	X	X
5. Influenza	X		X				X
6. Typhus		X	X		X	X	X
Long-term Visitors							
Above, plus:							
7. Plague†		X	X		X	X	
8. Rabies		X	X		X	X	X
9. BCG	X		X				X
10. Typhus	X‡	X	X		X	X	X

*For mandatory immunizations, see Table 1.

†For endemic or epidemic world foci, consult local USPHS quarantine authorities.

‡For the Balkans primarily.

Tuberculin-negative adults anticipating extended residence in developing countries, in close contact with endemic tuberculosis, should be offered BCG vaccine, particularly if they must work without benefit of close medical supervision. It should be remembered that BCG vaccination frequently will convert negative tuberculin reactions to positive ones. This, of course, renders ineffective any program for detection of early tuberculosis infection by periodic tuberculin test, and the possibility for periodic tuberculin testing should be kept in mind before BCG vaccine is given.

Finally, no review of requirements for immunization would be complete without consideration of the prophylaxis of infectious hepatitis. Although this cannot be done by active immunization, the incidence of clinical disease in susceptible adults appears to be significantly reduced by passive protection by conventional gamma globulin. A 5.0 ml. dose given intramuscularly and repeated once after five months is recommended for those making extended visits to areas where the risk of acquired infection is high. These include the countries of Asia, those of Africa, the Near East, the Indian subcontinent, and certain parts of Europe.

In summary, mandatory immunizations for foreign travel are few, consisting of vaccination against smallpox, and against yellow fever and cholera for those traveling to or from endemic areas. Other immunizations are not required by law, but are recommended on an area basis. The United States Public Health Service publishes a pamphlet, *Immunization Information for International Travel*, which can be procured from the Government Printing Office in Washington.

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